Modernized Classification of Cardiac Antiarrhythmic Drugs

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Cardiac arythmias

- Disorders of rate, rhythm, electrical impulse generation or conduction in the heart
- Arrhythmias are due to problems with the electrical conduction system of the heart
- Can involve abnormal ion channel function and defective intracellular ion handling
- Conditions may range from mild to life-threatning
- Many anti- arrhythmic drugs can aggravate or generate arrhythmia, leading to search for alternatives

anti-arrhythmic drugs

- The majority of currently available anti-arrhythmic drugs were specifically designed to target ion channels

- Anti-arrhythmic drug use has decreased over the past 15 years because of problems with side effects, particularly a paradoxical capacity to create more serious rhythm disorders than the ones being treated

- This phenomenon is called ‘proarrhythmia.

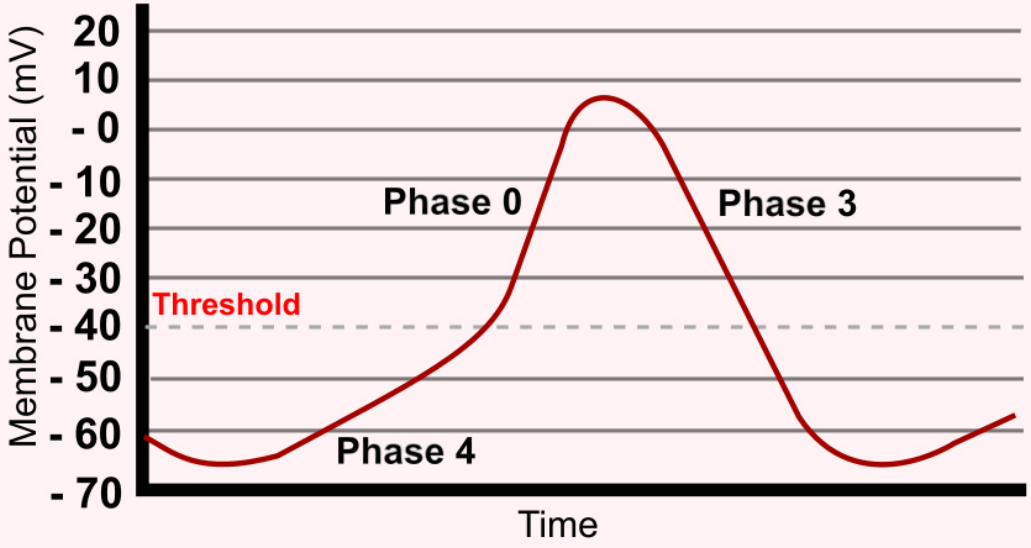
- Pro-arrhythmia is largely due to powerful effects of the drugs on ion channels, often in cardiac regions other than the arrhythmic zone being treated

Normal cardiac physiology

- The cellular basis of cardiac electrical activity is the cardiac action potential (AP), which is based on ion fluxes through specific membrane structures, particularly ion channels

- The ‘firing’ or depolarization of cardiac cells and closely associated cardiac electrical conduction depends on the movement of positive ions into the cell

Pacemaker Action Potential



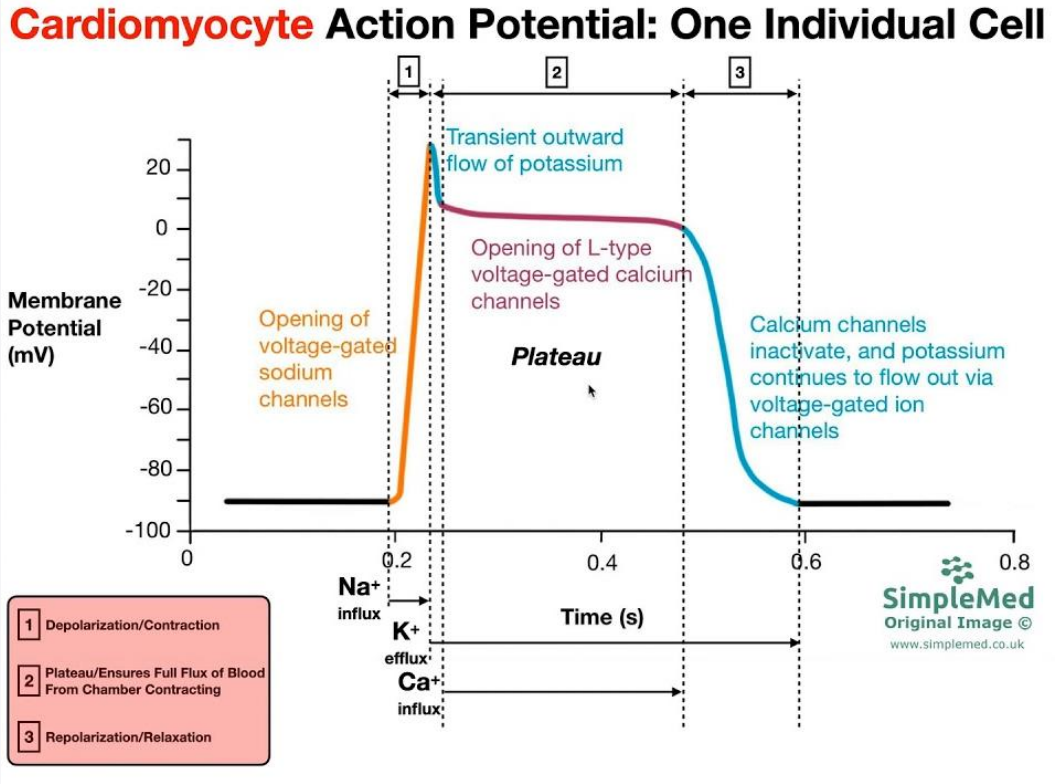
Ion Channels

Phase 4
- HCN "Funny" Current (If)
- T-type Calcium Channels

Phase 0
- L-type Calcium Channels (Primarily)

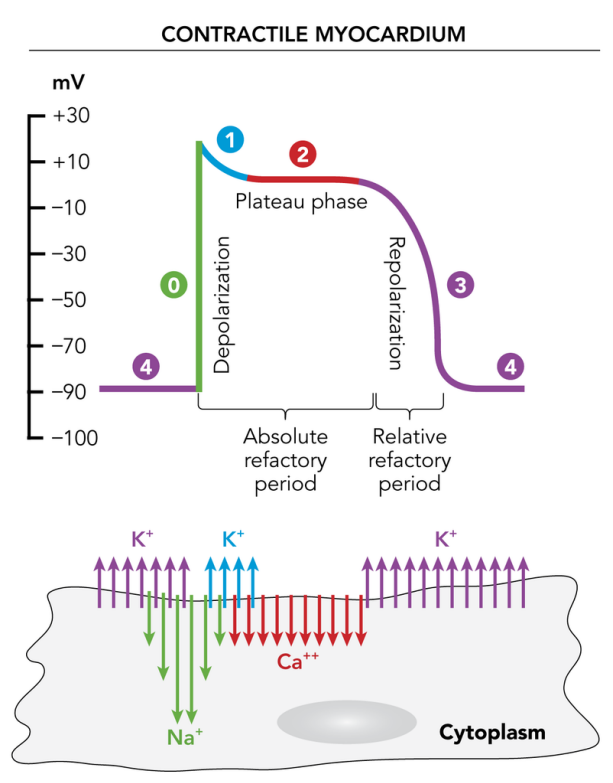
Phase 3
- Voltage-gated Potassium Channels

- Once a cardiac cell is fired by being depolarized from its normally negative resting intracellular potential to a positive value (causing a phase of the AP called ‘phase 0’), it goes through a series of regulated repolarizing steps (AP phases 1 and 3), separated by a relatively flat phase of the AP (phase 2), to get back to its resting potential.



- Cardiac cells are generally **inexcitable** once they have fired, and the time taken from initial depolarization to repolarization (called AP duration (APD)) imposes a limit (called the refractory period (RP)) on how soon a cell can be re-excited.

- APD is controlled by the rate of repolarization, which depends on the balance between **inward** movement of Na+ and Ca2+ that tends to keep the cell depolarized and **outward** movement of K+ through a series of highly specialized channels with typical time-dependent opening and closing properties.



Atrial fibrillation

In AF, the normal regular electrical impulses generated by the sinoatrial node are overwhelmed by disorganized electrical waves, usually originating from the roots of the pulmonary veins.

These disorganized waves conduct intermittently through the atrioventricular node, leading to irregular activation of the ventricles that generate the heartbeat.

The regular impulses produced by the sinus node for a normal heartbeat are overwhelmed by rapid electrical discharges produced in the atria and adjacent parts of the pulmonary veins.

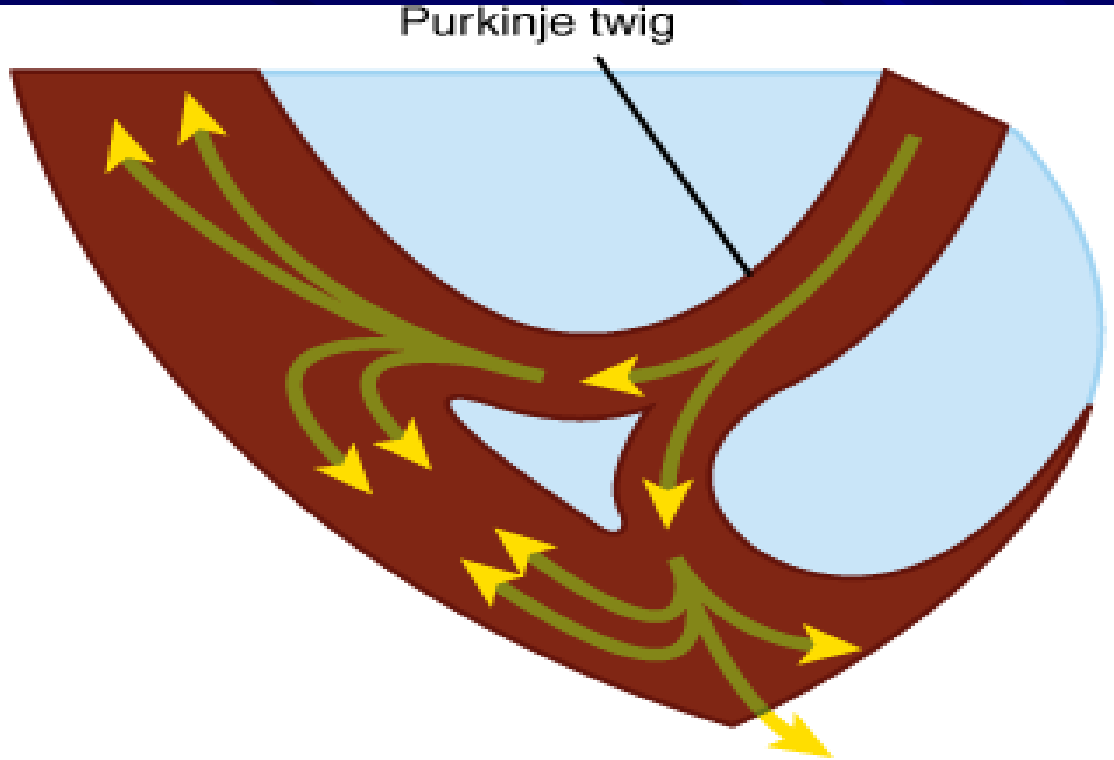
Sources of these disturbances are either automatic foci, often localized at one of the pulmonary veins, or a small number of localized sources in the form of either a re-entrant

Atrial fibrillation

in which one impulse reenters and excites areas of the heart more than once • The path of reentry may be confined to small areas (within or near the AV node), or it may involve a large area of atrial or ventricular walls.

Although the electrical impulses of AF occur at a high rate, most of them do not result in a heartbeat. A heartbeat results when an electrical impulse from the atria passes through the atrioventricular (AV) node to the ventricles and causes them to contract. During AF, if all of the impulses from the atria passed through the AV node, there would be severe ventricular tachycardia, resulting in a severe reduction of cardiac output.

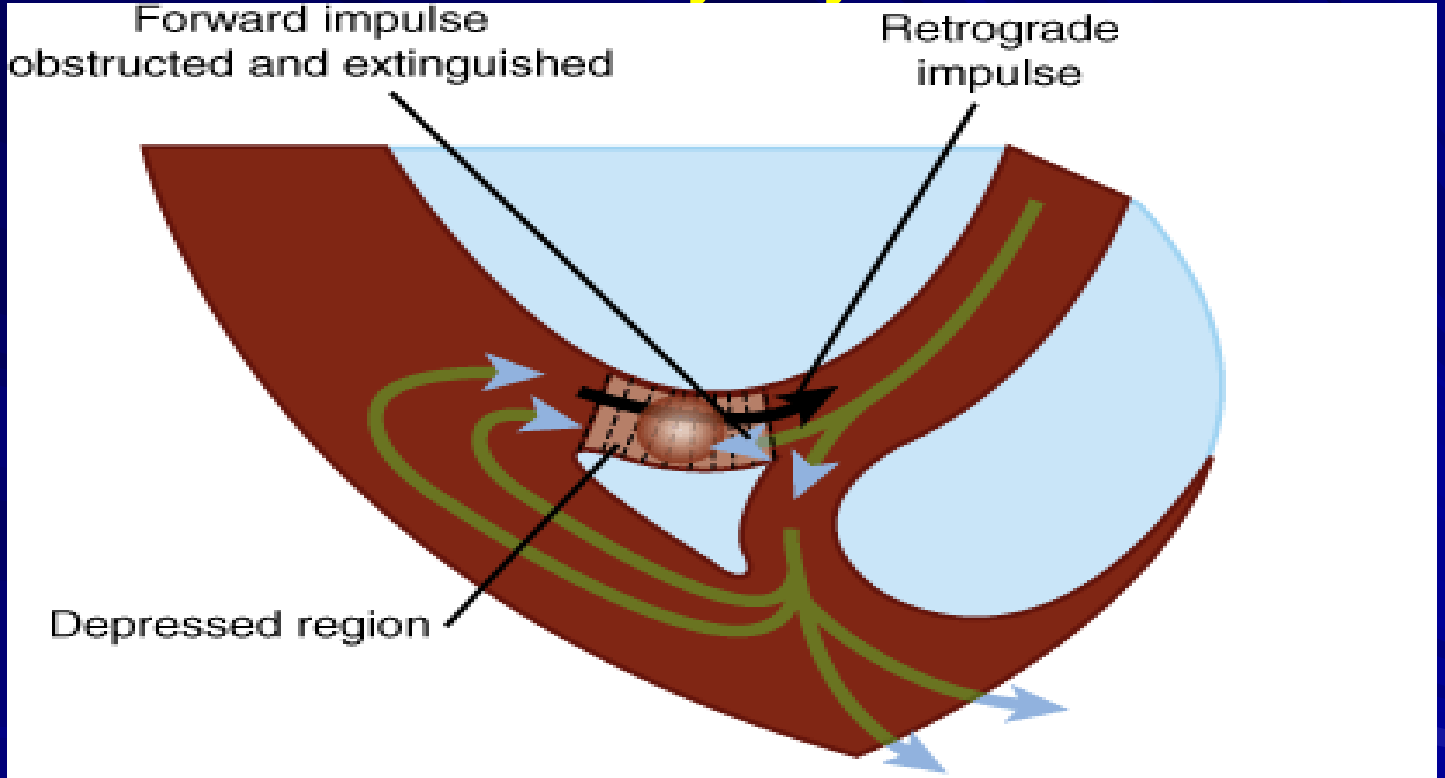
Normal Circuitry



A. Normal conduction

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Re-entry Rhythm



B. Unidirectional block

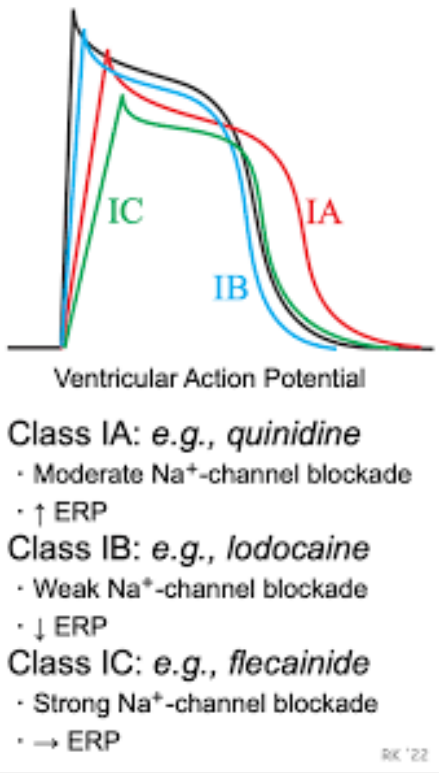
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Class I drugs

- Class I subcategories list cardiac **Na+ channel (Nav 1.5) blockers**
- The different Class I actions influence their clinical indications for arrhythmias affecting different regions of the heart
- **Class Id:** includes drug acting on recently reported **late Na currents**

Class Ia

- bind to the open state of Nav1.5 with moderate dissociation time constants (τ) of ≈1 to 10 seconds (moderate block)
- reduce AP conduction velocity
- increase ERP and APD
- Includes: quinidine, procainamide, disopyramide
- Clinical application: supraventricular tachyarrythmias (atrial fibrillation) and ventricular tachycaria

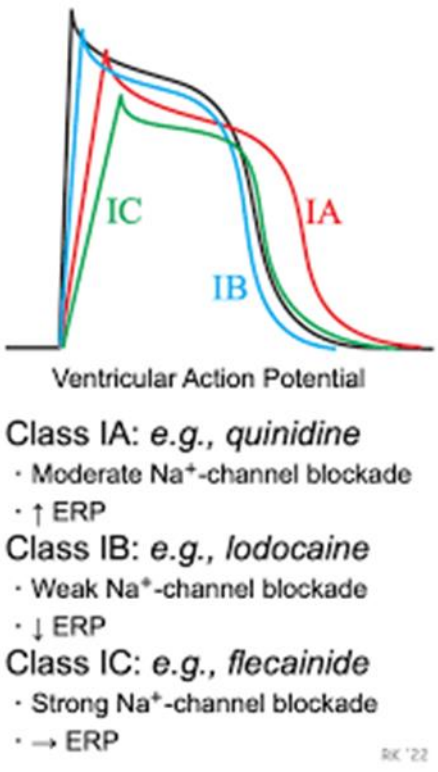


Side effects

- **Quinidine:**
  - Torsades de pointes with QT interval prolongation
  - GIT side effects: diarrhea, nausea, vomiting
  - Cinchonism: a syndrome of headache, dizziness and tinnitus
  - May increase the plasma concentration of digoxin leading to digitalis toxicity
- **Procainamide:**
  - Torsades de pointes with prolonged QT interval
  - Lupus-like syndrome: rash, small joint arthralgia, and arthritis
  - Pleuritis and pericarditis
  - Hypotension
  - Nauses, vomiting, fever, hepatitis

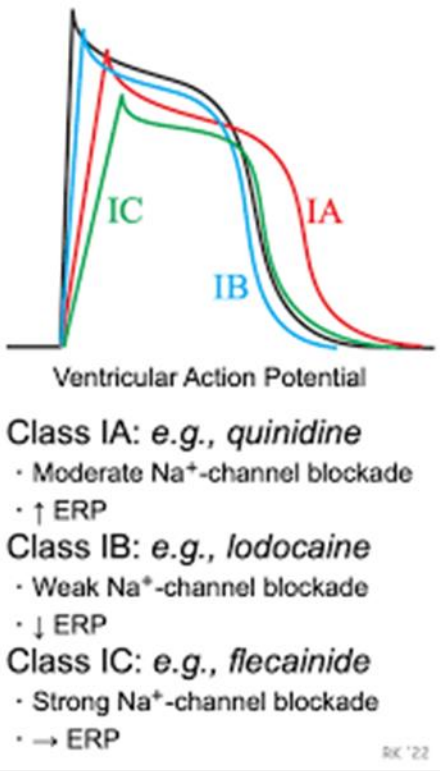
Class Ib

- drugs bind to the Nav1.5 **inactivated** state with relatively rapidly dissociation time constant τ of ≈0.1 to 1.0 second (weak block)
- shortens both APD and ERP in normal ventricular muscle and Purkinje cells
- Includes: lidocaine
- Clinical applications: Ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation)
- **Side effects**: CNS effects (slurred speech, drownsiness, dizziness, muscle twitching, seizures)



Class Ic

- Also bind to the inactivated Nav1.5, from which they dissociate more slowly, over τ >10 seconds (marked block)
- Reduce AP conduction velocity
- Maintain normal ERP and APD
- Include: propafenone, flecainide
- Clinical applications:
  - Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation);
  - Ventricular tachyarrhythmias resistant to other treatment



Class Ic Side effects

- **Flecainide:**
  - Ventricular tachycardia in presence of ischemic heart disease or old MI
  - Vision problems
  - Headache, dizziness
  - Has been shown to have teratogenic effects
- **Propafenone:**
  - Ventricular tachycardia in presence of ischemic heart disease or old MI
  - Slowed sinus rate
  - Dizziness, chest pain, shortness of breath
  - N/V, constipation/ diarrhea

Class II

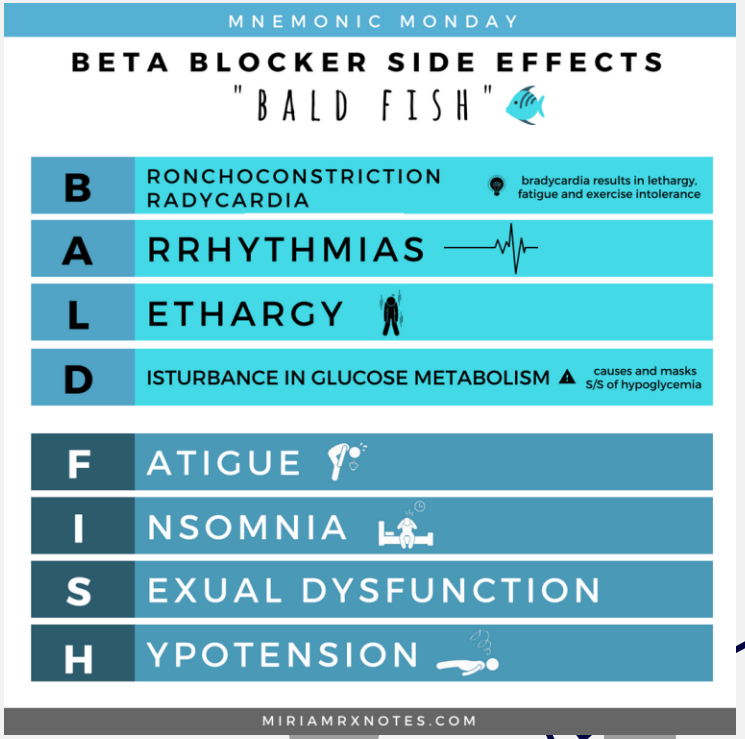
- Class II extends its coverage beyond an updated range of sympathetic β-adrenergic effects to further include **parasympathetic targets.**
- **Beta adrenergic receptors:**
  - β-adrenergic receptor activation causes successive Gs -protein and adenylate cyclase activation leading to increased cytosolic [cAMP]
  - The increased [cAMP]i activates protein kinase A, which phosphorylates a wide range of ion channels
  - cAMP also exerts a direct influence on hyperpolarization-activated cyclic nucleotide-gated channel activity and consequently on the pacemaking funny current [I f]
  - Finally, exchange proteins directly activated by cAMP have been reported to trigger RyR2-mediated Ca2+ release.

Class IIa

- Includes nonselective and selective β1 -adrenergic receptor **inhibitors** (beta blockers)
- Examples: Nonselective: **carvedilol and propranolol;** selective: **atenolol, metoprolol**
- Clinical indiction: indicated in a wide range of tachyarrhythmias (sinus tachycardia, supraventricular and ventricular tachyarrythmias)
- Cause reduction in SAN automaticity; Reduction in AVN automaticity; Reduction in ectopic ventricular/atrial automaticity

Side effects of beta blockers

- Up regulation of beta- receptors with long term therapy, beta blocker withdrawal
- Sinus bradycardia, AV block
- Cold extremities
- Masks symptoms of hypoglycemia



Class IId

- Muscarinic M2 receptor activators
- Examples: **digoxin**
- Digoxin has *two principal mechanisms of action*, which are selectively employed depending on the indication:

1. **Positive ionotropic**: It increases the force of contraction of the heart by reversibly inhibiting the activity of the myocardial Na-K ATPase pump. Digoxin induces an increase in intracellular sodium that will drive an influx of calcium in the heart and cause an increase in contractility. Cardiac output increases with a subsequent decrease in ventricular filling pressures.
2. **AV node inhibition**: Digoxin activates supraventricular M2 cholinergic receptors (parasympathetic nervous system activation), it slows electrical conduction in the atrioventricular node, therefore decreasing the heart rate.

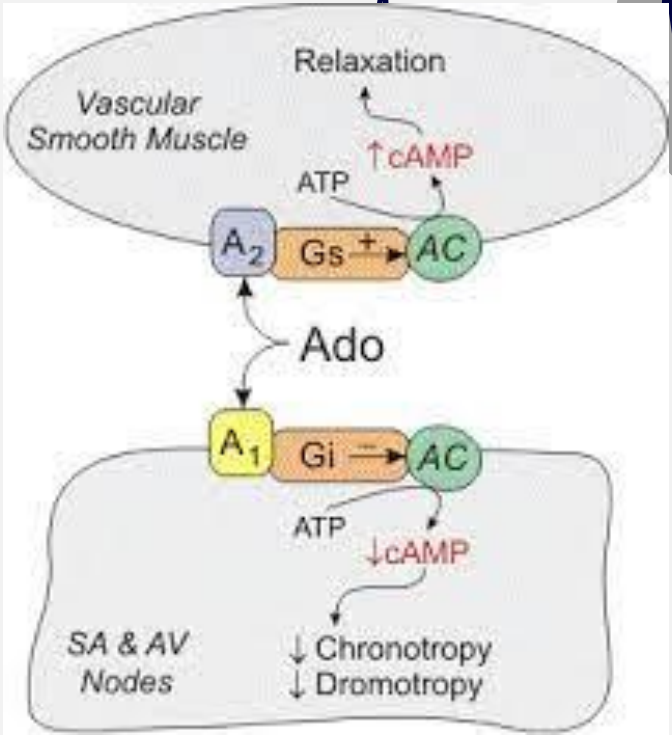
- Clinical indications: Sinus tachycardia or supraventricular tachyarrhythmias

Digoxin adverse effects

- Visual changes (blurring, photophobia, disturbance in vision color)
- GI toxicity: anorexia, nausea, vomiting
- Gynaecomastia, skin rashes
- Cardia adverse effects:
  - Bradycardia
  - AV block
  - Paroxysmal atrial tachycardia
  - Sino atrial arrest
  - Ventricular tachycardia

Class IIe

- Adenosine A1 receptor activators
- Examples: **Adenosine, ATP**
- MOA: Adenosine exerts a negative chronotropic effect by suppressing the automaticity of cardiac pacemakers, and a negative dromotropic effect through inhibition of AV-nodal conduction
- Clinical indications: Acute termination of AVN tachycardia and cAMP mediated triggered VTs



Adenosine side effects

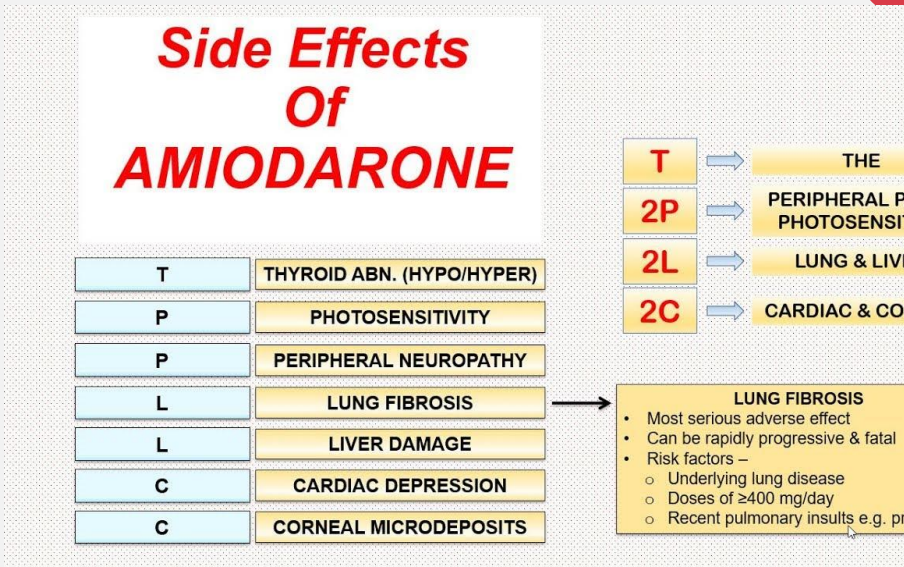
- Sinus bradycardia, sinus arrest or AV block
- Atrial fibrillation
- Diarrhea.
- feeling of warmth.
- indigestion.
- loss of appetite.
- nausea or vomiting.
- redness of the face, neck, arms, and occasionally, upper chest.
- stomach pain, fullness, or discomfort.

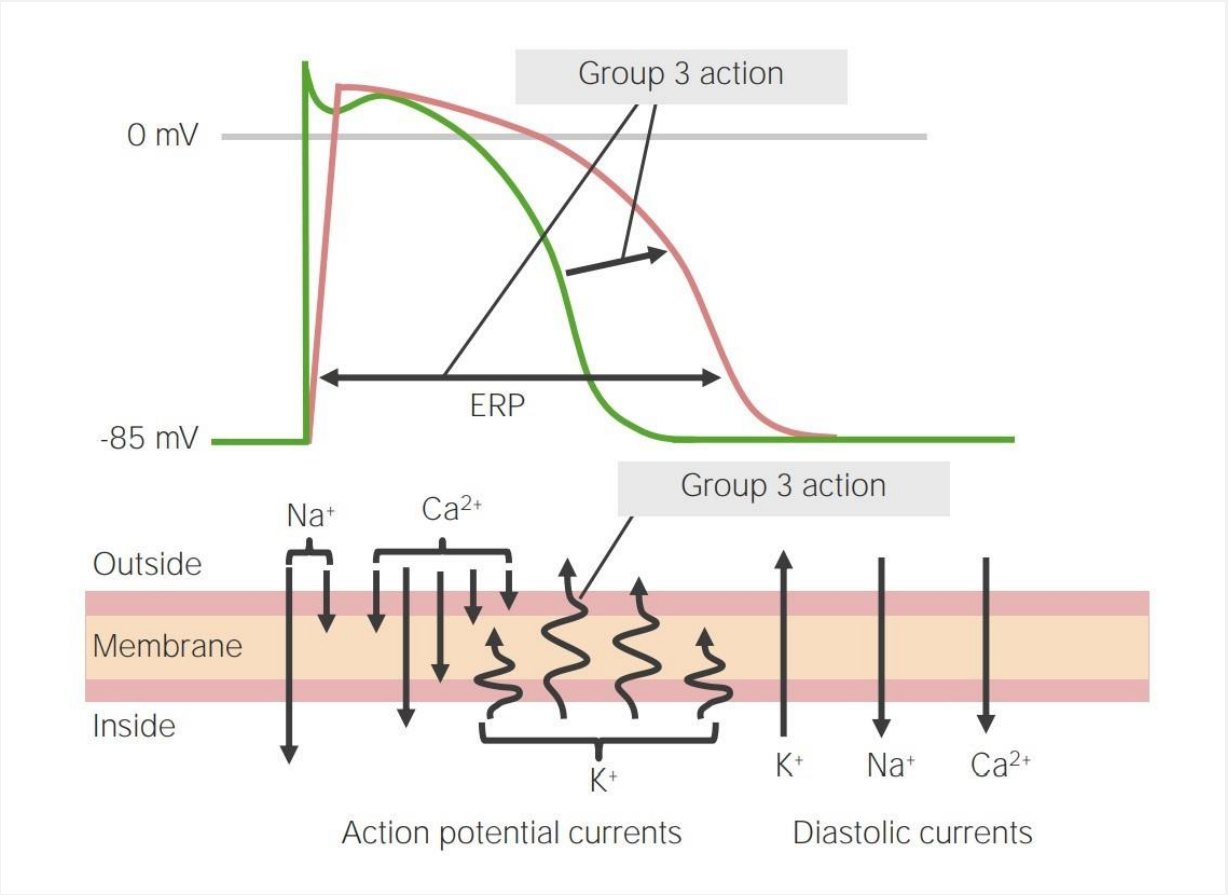
Class III

- After phase 0 depolarization, complex components of transient inward current (I to) contribute to early rapid phase 1 AP repolarization.
- Class III agents includes wider ranges of voltage-dependent **K+ channel blockers**
- Examples: nonselective (**ambasilide, amiodarone**) and selective (**dofetilide, ibutilide, sotalol**) blockers
- They block multiple K+ channel targets resulting in prolonged atrial, Purkinje, and/or ventricular myocyte AP recovery, increased ERP, and reduced repolarization reserve

Class III side effects

- Torsades de pointes with QT prolongation Heart failure.
- Heart block
- Bradycardia




Group 3 action
0 mV
ERP
-85 mV
Group 3 action
Na+
Ca2+
Outside
Membrane
Inside
K+
K+
Na+
Ca2+
Action potential currents
Diastolic currents

Class IV

- The central importance of Ca2+ homeostasis to cardiac electrophysiological activity accounts for a wide range of potential applications directed at clinical arrhythmia
- Originally defined as **drugs blocking Ca2+ entry** through specific Ca2+ channels (CCB)
- It was extended to include drugs with a variety of actions that can be described as Ca2+ handling modulators

Class IVa

- Surface membrane Ca2+ channel blockers
- Examples:
  - non-selective:**Bepridi**l
  - Selective: Phenylalkylamines (eg, **verapamil**), benzothiazepines (eg, **diltiazem**)
- MOA: Block of Ca2+ current (I Ca), resulting in inhibition of SAN pacing, inhibition of AVN conduction, prolonged ERP, increased AP recovery time, increased refractory period