ANTI-ARRHYTHMIC AGENTS

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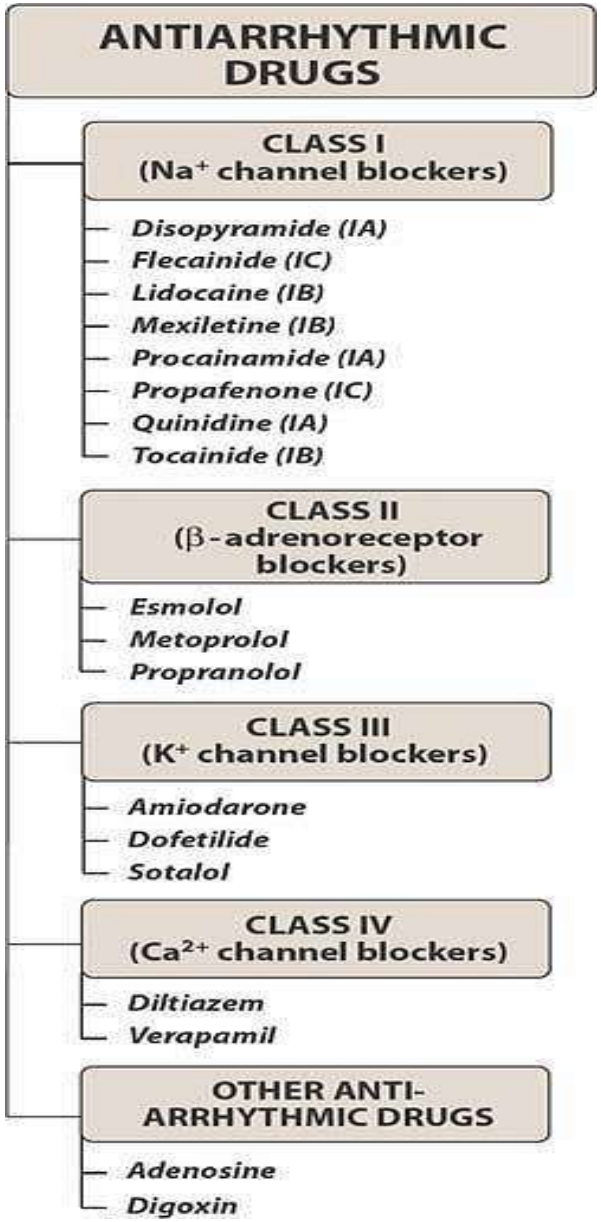
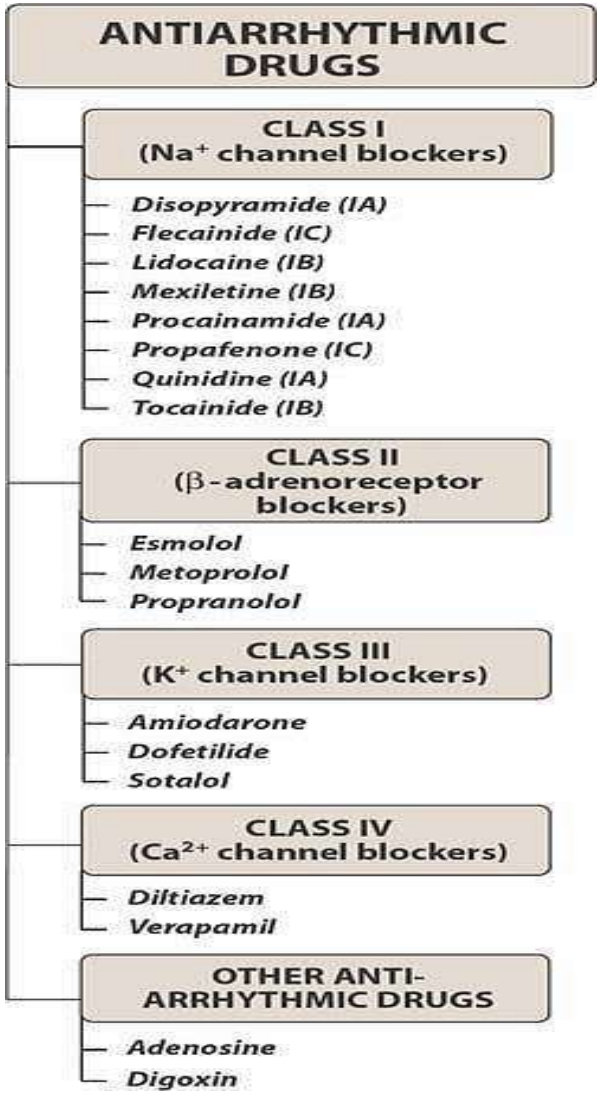


Arrhythmia

- An arrhythmia is a problem with the rate or rhythm of the heartbeat (irregular heartbeat) . During an arrhythmia, the heart can beat too fast, too slow, or with an irregular rhythm.
- A heartbeat that is too fast is called tachycardia. A heartbeat that is too slow is called bradycardia.

B. Antiarrhythmic drugs

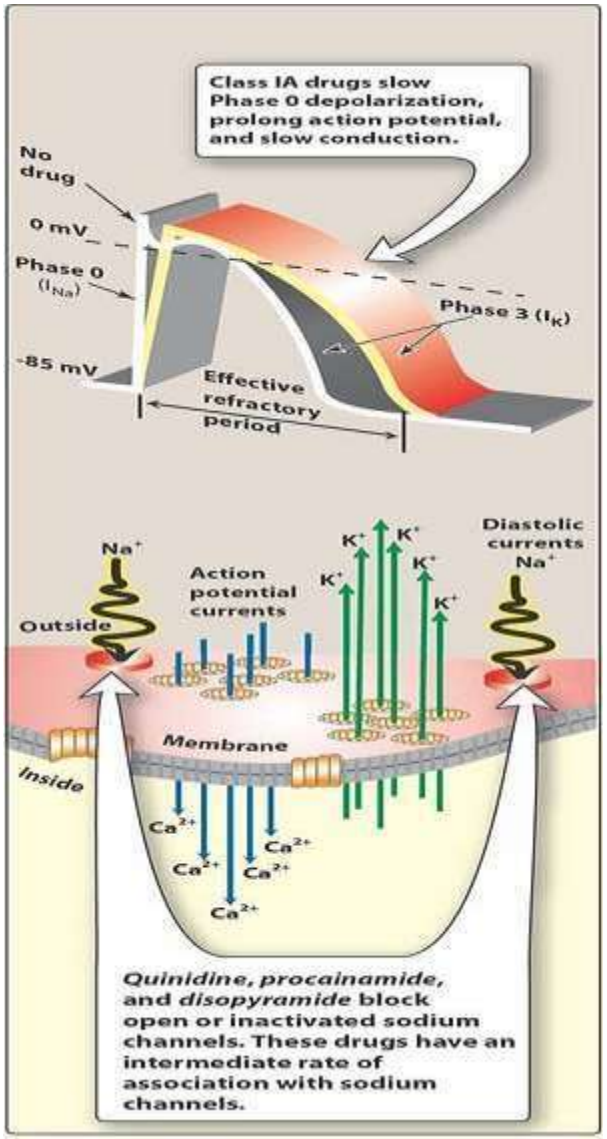


III. Class I Antiarrhythmic Drugs

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

Quinidine IA

- Therapeutic uses: Quinidine is used in the treatment of a wide variety of arrhythmias, including atrial, AV-junctional, and ventricular tachyarrhythmias. Quinidine is used to maintain sinus rhythm after direct-current cardioversion of atrial flutter or fibrillation and to prevent frequent ventricular tachycardia.
- Pharmacokinetics: Quinidine sulfate is rapidly and almost completely absorbed after oral administration. It undergoes extensive metabolism by the hepatic cytochrome P450 enzymes, forming active metabolites.

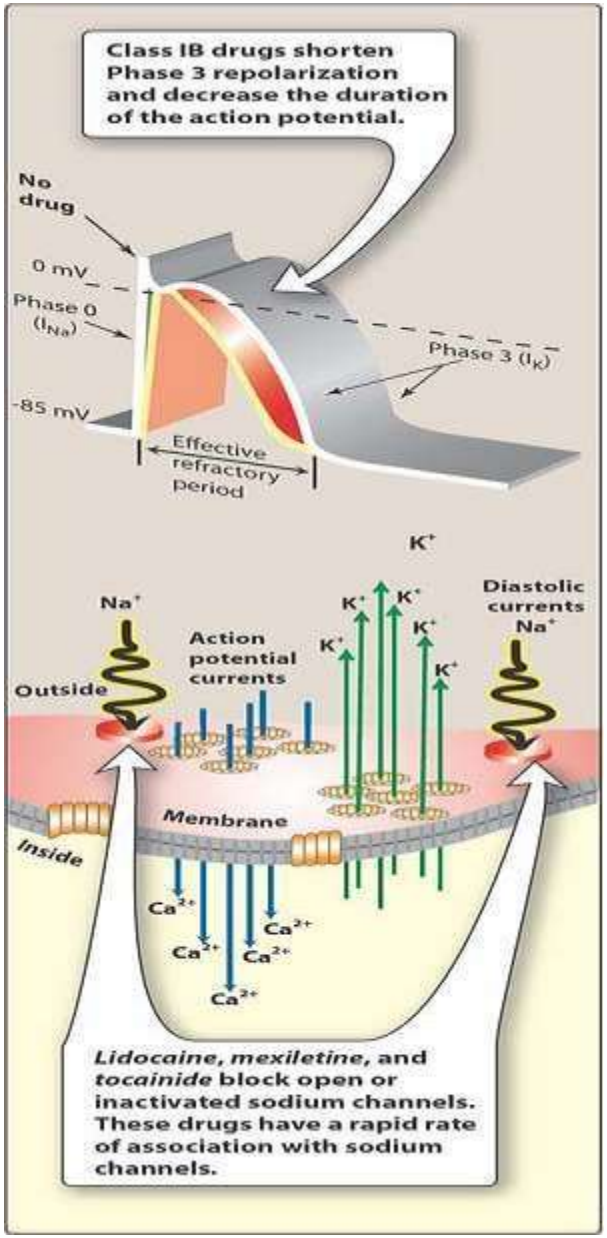


Adverse effects

- Quinidine may cause SA and AV block or asystole.
- At toxic levels, the drug may induce ventricular tachycardia. Cardiotoxic effects are exacerbated by hyperkalemia.
- Nausea, vomiting, and diarrhea are commonly observed.
- Large doses of quinidine may induce the symptoms of cinchonism (for example, blurred vision, tinnitus, headache, disorientation, and psychosis).

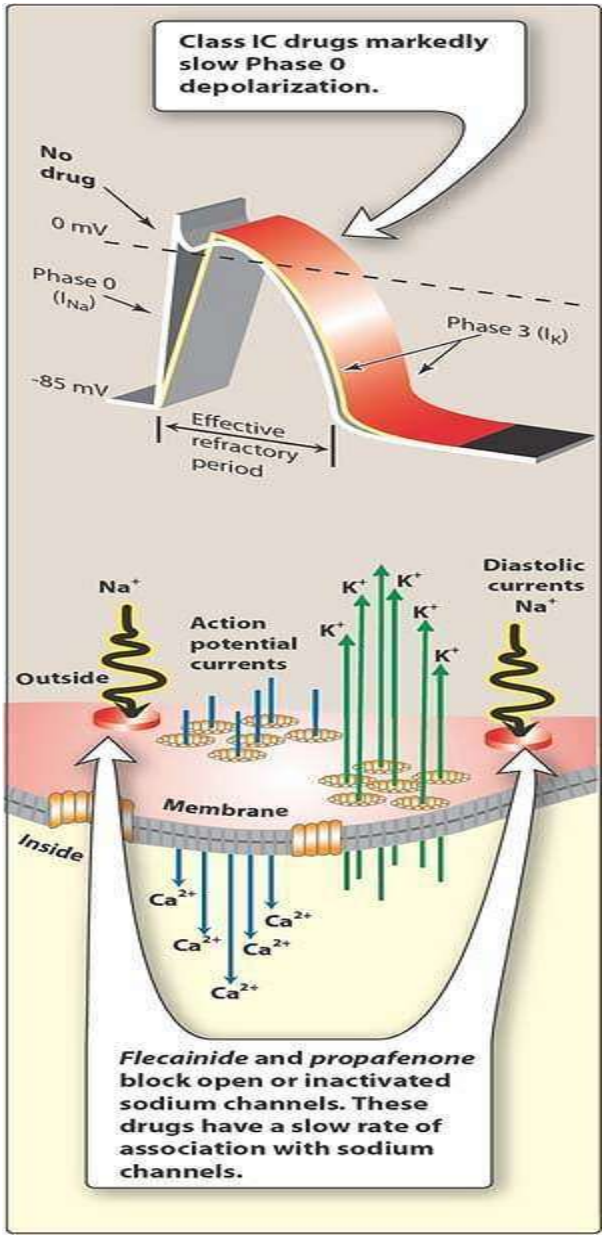
Mexiletine and Tocainide IB

- These Class IB drugs have actions similar to those of lidocaine, and they can be administered orally. Mexiletine is used for chronic treatment of ventricular arrhythmias associated with previous myocardial infarction. Tocainide is used for treatment of ventricular tachyarrhythmias. Tocainide has pulmonary toxicity, which may lead to pulmonary fibrosis.



H. Flecainide IC

- Therapeutic uses: Flecainide is useful in treating refractory ventricular arrhythmias. It is particularly useful in suppressing premature ventricular contraction. Flecainide has a negative inotropic effect and can aggravate congestive heart failure.
- Pharmacokinetics: Flecainide is absorbed orally, undergoes minimal biotransformation, and has a half-life of 16 to 20 hours.
- Adverse effects: Flecainide can cause dizziness, blurred vision, headache, and nausea. Like other Class IC drugs, flecainide can aggravate preexisting arrhythmias or induce life-threatening ventricular tachycardia that is resistant to treatment.



Class II Antiarrhythmic Drugs

- Class II agents are **β-adrenergic antagonists**. These drugs diminish Phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility.
- Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity. They are also used for atrial flutter and fibrillation and for AV-nodal reentrant tachycardia.
- In contrast to the sodium-channel blockers, β-blockers and Class III compounds, such as sotalol and amiodarone, are increasing in use.

A. Propranolol

Propranolol reduces the incidence of sudden arrhythmic death after myocardial infarction (the most common cause of death in this group of patients). The mortality rate in the first year after a heart attack is significantly reduced by propranolol, partly because of its ability to prevent ventricular arrhythmias.

B. Metoprolol

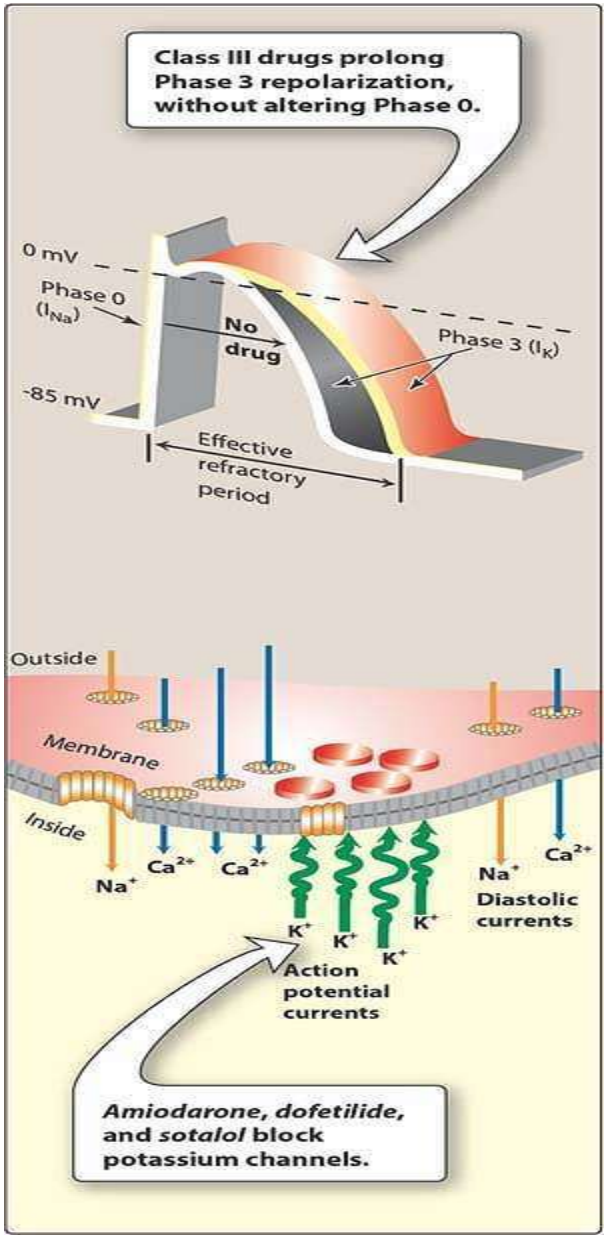
Metoprolol is the β-adrenergic antagonist most widely used in the treatment of cardiac arrhythmias.
Compared to propranolol, it reduces the risk of bronchospasm.

C. Esmolol

Esmolol is a very short-acting β-blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations.

Amiodarone III

- Therapeutic uses: Amiodarone is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias. Despite its side-effect profile, amiodarone is the most commonly employed antiarrhythmic.
- Pharmacokinetics: Amiodarone is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half-life of several weeks, and it distributes extensively in adipose issue. Full clinical effects may not be achieved until 6 weeks after initiation of treatment.



Adverse effects

- Amiodarone shows a variety of toxic effects. After long-term use, more than half of patients receiving the drug show side effects that are severe enough to prompt its discontinuation.
- Some of the more common effects include interstitial pulmonary fibrosis, gastrointestinal tract intolerance, tremor, ataxia, dizziness, hyper- or hypothyroidism, liver toxicity, photosensitivity, neuropathy, muscle weakness, and blue skin discoloration caused by iodine accumulation in the skin.

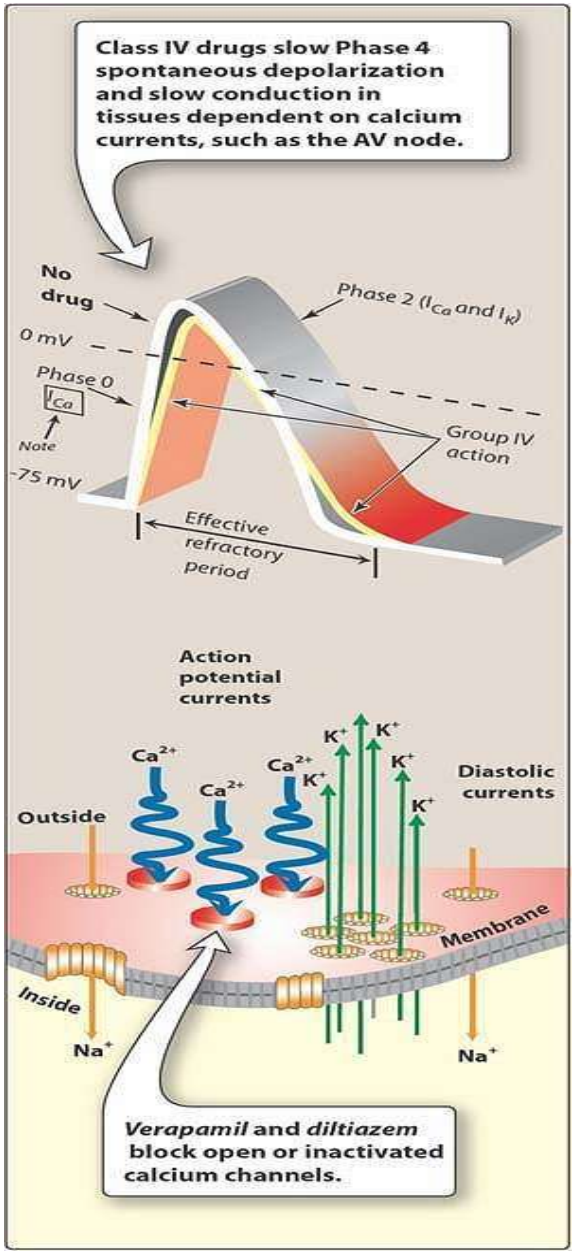
Dofetilide III

- Dofetilide can be used as a **first-line** antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease with impaired left ventricular function.
- Because of the risk of proarrhythmia, dofetilide initiation is limited to the inpatient setting and is restricted to prescribers who have completed a specific manufacturer's training session. Along with amiodarone and β- blockers, dofetilide is the only antiarrhythmic drug that is recommended by experts for the treatment of atrial fibrillation in a wide range of patients.
- The half-life is 10 hours. Excretion is in the urine, with 80 percent as unchanged drug and 20 percent as inactive or minimally active metabolites.

Verapamil and diltiazem (IV)

Therapeutic uses: Verapamil and diltiazem are more effective against atrial than against ventricular arrhythmias. They are useful in treating reentrant supraventricular tachycardia and in reducing the ventricular rate in atrial flutter and fibrillation. In addition, these drugs are used to treat hypertension and angina.

Pharmacokinetics: Verapamil and diltiazem are absorbed after oral administration. Verapamil is extensively metabolized by the liver; thus, care should be taken when administering this drug to patients with hepatic dysfunction.



Adverse effects:

- Verapamil and diltiazem have negative inotropic properties and, therefore, may be **contraindicated** in patients with preexisting depressed cardiac function. Both drugs can also produce a decrease in blood pressure because of peripheral vasodilation an effect that is actually beneficial in treating hypertension.

Other Antiarrhythmic Drugs

- **Digoxin** shortens the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in the AV node.

  Digoxin is used to control the ventricular response rate in atrial fibrillation and flutter.

  At toxic concentrations, digoxin causes ectopic ventricular beats that may result in ventricular tachycardia and fibrillation.

- Adenosine is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node. Intravenous adenosine is the drug of choice for abolishing acute supraventricular tachycardia. It has low toxicity but causes flushing, chest pain, and hypotension. Adenosine has an extremely short duration of action (approximately 15 seconds).