

Management of angina and heart failure

I-Introduction

The pharmacological management of angina and heart failure focuses on reducing symptoms, preventing complications, and improving quality of life. For **angina**, this involves medications like **nitrates**, **beta-blockers**, and **calcium channel blockers** to reduce myocardial oxygen demand. In **heart failure**, **diuretics**, **ACE inhibitors/ARBs**, **beta-blockers**, and other drugs like SGLT2 *(**Sodium-Glucose Cotransporter-2**) inhibitors and **ARNIs (Angiotensin receptor/neprilysin inhibitors)** are used to improve cardiac function and reduce symptoms. **Arrhythmias** are treatable with medicine or procedures to control the irregular rhythms.

If not treated, arrhythmias can damage the heart, brain, or other organs. This can lead to life-threatening stroke, heart failure, or cardiac arrest. During cardiac arrest, the heart suddenly and unexpectedly stops beating, causing death if it is not treated within minutes.

Types of arrhythmia:

- 1- Bradycardia is a resting heart rate that is slower than 60 beats per minute.
- 2- Tachycardia is a resting heart rate that is faster than 100 beats per minute.
- 3- A premature or extra heartbeat happens when the signal to beat comes too early.

Treatment of angina:

Three basic groups of treatment:

1. Treatment that aims at immediate relief – Mainly drugs are used for this target achievement.
2. Treatment that reduces the frequency of attacks – Medications are the mainstay for this target as well.
3. Treatment that reduces the risk of heart attacks and strokes – Both medication and surgery may be used to achieve this target.

1-Treatment that aims at immediate relief:

Glyceryl trinitrate (GTN) is the most common drug used for this purpose. It belongs to the class of Nitrates. There are various Nitrate preparations. These act by increasing the blood vessel diameter by relaxing the muscles of the vessel walls and relieve the obstruction reducing the symptoms of angina.

GTN may be given as a patch to be applied over the skin. Alternatively they are administered as a pill which is placed underneath the tongue for rapid absorption.

GTN usually eases the pain within two to three minutes. If the first dose does not work, a second dose can be taken after five minutes and a third dose after a further five minutes.

If GTN fails to relieve pain after 15 minutes, unstable angina should be suspected and patient should be moved for urgent medical help.

Adverse effects:

GTN may cause some headaches and dizziness. This occurs due to a fall in blood pressure due to widening of blood vessels of the head and whole body. Driving and operating heavy machinery should be avoided when GTN is taken.

2- Treatment that reduces the frequency of attacks:

Several medications are available for this purpose. These include:

a- Calcium Channel Blockers (CCBs):

These act by relaxing the muscles that line the blood vessels of the heart and the body. In the heart they lead to easing up of the narrowed coronary arteries and thus reduce the frequency of attacks of angina. Drugs include **Amlodipine, Nifedipine** etc.

Adverse effects:

They may lead to side effects like dizziness (due to fall in blood pressure), edema of the feet, flushed face, headaches, and tiredness and skin rashes (due to allergies). These usually are relieved with use and do not require therapy.

b- Beta-blockers

These drugs are important for treatment of high blood pressure. They include drugs like Atenolol, Metoprolol etc. These act by reducing the blood pressure and heart rate. Both of these mechanisms reduce the oxygen requirement of the heart muscles and thus reduce the frequency of the angina attacks.

Adverse effects:

Common side effects include dizziness, tiredness, cold feet and hands, nausea etc. These are usually resolved with time. Older beta blockers like Propranolol may lead to exacerbation of symptoms of asthma and are not prescribed in angina.

Long-acting nitrates:

These include drugs like **Isosorbide mononitrate and Isosorbide dinitrate**. These drugs also relax the blood vessels and improve blood flow to the heart and reduce the frequency of attacks. Their side effects are similar to GTN.

Ivabradine

This is a newer agent used in angina routinely these days. This acts like beta blockers by slowing down the speed of the heart and reducing cardiac muscle oxygen demand.

Ivabradine may be used in patients who cannot use beta blockers. A common side effect of ivabradine is vision difficulties.

Nicorandil

This drug acts by opening up tiny channels within the cells that transmit Potassium. This falls under a group Potassium channel activators. These have similar effects as CCBs and increase the blood flow to the heart.

These drugs may be used as an alternative to CCBs. Side effects include dizziness and headaches that are resolved with long term usage.

Ranolazine

This relaxes the heart muscles and improves the blood flow to reduce the frequency of angina attacks. Ranolazine use is associated with weakness, dizziness and constipation.

Many patients are managed with single drugs while some may require combination therapy for better efficacy. When symptoms fail to ease with two drug groups, patient may be recommended for surgery.

3- Treatment that reduces the risk of heart attacks and strokes:

Treatments that reduce the risk of heart attacks and strokes include:

a- Cholesterol-lowering drugs

Drugs that lower the bad cholesterol include statins. Over long term these drugs like Atorvastatin, Pravastatin, Lovastatin, Rosuvastatin etc. help prevent atherosclerosis of the coronary arteries. These act by blocking an enzyme in the liver that is essential for production of cholesterol.

Side effects of statin use are liver damage, muscle aches.

b- Antiplatelet agents

These include **Aspirin** in low doses. These agents reduce the propensity of platelets to form clots and obstruct the arteries as the atherosclerotic plaques rupture.

Aspirin in low dose (75 mg per day) reduces the risk of a heart attack in susceptible individuals. All angina patients especially those with unstable angina are prescribed low dose Aspirin.

Common side effects include stomach ulcer and indigestion. Patients who are unable to take Aspirin may be given other Antiplatelet agents like Clopidogrel.

4- Angiotensin-converting enzyme (ACE) inhibitors:

These drugs are commonly used in high blood pressure patients and those with diabetes and high blood pressure. Over long term these drugs including Enalapril, Captopril, Lisinopril etc. help in reduction of cardiac muscle damage by the angina and reduce the risk of heart attacks.

Side effects include allergic reactions and cough. Pregnant women cannot take these drugs as they may damage the kidneys of the unborn fetus.

Management of arrhythmia

Introduction:

An arrhythmia (also called dysrhythmia) is an abnormal heartbeat . Arrhythmias can start in different parts of your heart and they can be too fast, too slow or just irregular.

Normally, your heart beats in an organized, coordinated way. Issues with various parts of your heart — or even the blood your heart pumps — can affect your heart’s normal rhythm. Having a normal heart rhythm matters because your heart supplies your whole body with nutrients and oxygen through the blood it pumps.

Your heart rate is how many times your heart beats in 60 seconds. This number can go up or down as you go through your day.

Treatment:

Common arrhythmia treatments include medicines, surgery to implant devices that control your heartbeat, and other procedures to treat problems with electrical signals in your heart. You may also need to make healthy lifestyle changes to help lower your risk of conditions that can make your arrhythmia worse, such as high blood pressure and other types of heart disease.

How are arrhythmias treated?

Medicine to treat a slow heartbeat (such as **atropine**) may be given by emergency medical services (EMS) or in the emergency room (ER). Atropine may cause difficulty swallowing.

Medicines to treat a fast heartbeat include:

- **Adenosine**, which can cause some chest pain, flushing, shortness of breath, and atrial fibrillation and may be given by EMS or in the ER
- **Beta blockers**, which can cause fatigue, stomach or sleep problems, and sexual dysfunction, and can make some conduction disorders worse
- **Calcium channel blockers**, which can cause digestive trouble, swollen feet, or low blood pressure
- **Digoxin**, which is used to treat atrial fibrillation, and can cause nausea, vomiting, and diarrhea
- **Potassium channel blockers**, which can cause low blood pressure, problems with your thyroid levels, lung conditions, or another type of arrhythmia
- **Sodium channel blockers**, which raise the risk of sudden cardiac arrest in people who have heart disease.

Antiarrhythmic drugs:

Antiarrhythmic drugs Antiarrhythmic drugs can modify impulse generation and conduction to prevent arrhythmias from occurring or to reduce symptoms associated with arrhythmias. They were classified into four categories:

1- CLASS I: ANTIARRHYTHMIC DRUGS:

Class I antiarrhythmic drugs act by blocking voltage- sensitive sodium (Na⁺) channels. The use of sodium channel blockers has declined due to their proarrhythmic effects. The class I drugs have been subdivided into three groups according to their effect on the duration of the ventricular action potential (Table 1).

A- antiarrhythmic drugs: Quinidine, procainamide, and disopyramide

Quinidine is the prototype class IA drug. Other agents in this class include procainamide and disopyramide. Because of their concomitant class III activity, they can precipitate arrhythmias that can progress to ventricular fibrillation.

Mechanism of action:

- Quinidine binds to open and inactivated sodium channels and prevents sodium influx, thus slowing the rapid upstroke during phase 0 (Figure 3).

- It decreases the slope of phase 4 spontaneous depolarization, inhibits potassium channels, and blocks calcium channels. Because of these actions, it slows conduction velocity and increases refractoriness.
- Procainamide and disopyramide have actions similar to those of quinidine.

Therapeutic uses:

- Quinidine is used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias.
- Procainamide is available in an intravenous formulation only and may be used to treat acute atrial and ventricular arrhythmias. However, amiodarone has mostly replaced procainamide in clinical use.
- Disopyramide is used in the treatment of ventricular arrhythmias as an alternative to procainamide or quinidine and may also be used for maintenance of sinus rhythm in atrial fibrillation.

Adverse effects:

- Large doses of quinidine may induce the symptoms of cinchonism (for example, blurred vision, tinnitus, headache, disorientation, and psychosis).
 - Drug interactions are common with quinidine since it is an inhibitor of both CYP2D6 and P-glycoprotein.
- Intravenous administration of procainamide may cause hypotension.
- As disopyramide has anticholinergic action more than the other drugs in this class, it shows the most anticholinergic adverse effects of the class IA drugs (for example, dry mouth, urinary retention, blurred vision, and constipation).

B- antiarrhythmic drugs: Lidocaine

- The class IB agents rapidly associate and dissociate from sodium channels. Thus, the actions of class IB agents are manifested when the cardiac cell is depolarized or firing rapidly.
- The class IB drug lidocaine is useful in treating ventricular arrhythmias.

- In addition to sodium channel blockade, lidocaine shortens phase 3 repolarization and decrease the duration of the action potential (Figure 3).

Therapeutic uses:

- Although amiodarone has supplanted lidocaine for use in ventricular fibrillation or pulseless ventricular tachycardia (VT), lidocaine may be useful as an alternative.
- Lidocaine may also be used in polymorphic VT or in combination with amiodarone for VT storm. The drug does not markedly slow conduction and, thus, has little effect on atrial or AV junction arrhythmias.

Pharmacokinetics

- Lidocaine is given intravenously because of extensive first-pass transformation by the liver, which precludes oral administration.

Adverse effects:

- Lidocaine has a fairly wide therapeutic index. It shows little impairment of left ventricular function and has no negative inotropic effect.
- CNS effects include nystagmus (early indicator of toxicity), drowsiness, slurred speech, agitation, confusion, and convulsions, which often limit the duration of continuous infusions.

C- antiarrhythmic drugs: Flecainide and propafenone

These drugs slowly dissociate from resting sodium channels and show prominent effects even at normal heart rates. Several studies have cast serious doubts on the safety of the class IC drugs, particularly in patients with structural heart disease.

Mechanism of action:

- Flecainide suppresses phase 0 upstroke in Purkinje and myocardial fibres. This causes marked slowing of conduction in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness.
- Automaticity is reduced by an increase in the threshold potential, rather than a decrease in slope of phase 4 depolarization.
- Flecainide also blocks potassium channels leading to increased action potential duration, even more so than propafenone.

- Propafenone, like flecainide, slows conduction in all cardiac tissues but does not block potassium channels.

Therapeutic uses:

Flecainide is useful in the maintenance of sinus rhythm in atrial flutter or fibrillation in patients without structural heart disease and in treating refractory ventricular arrhythmias. Use of propafenone is restricted mostly to atrial arrhythmias. A schematic summary about class I antiarrhythmic drugs effect on the action potential of a cardiac myocyte is summarised in figure 3.

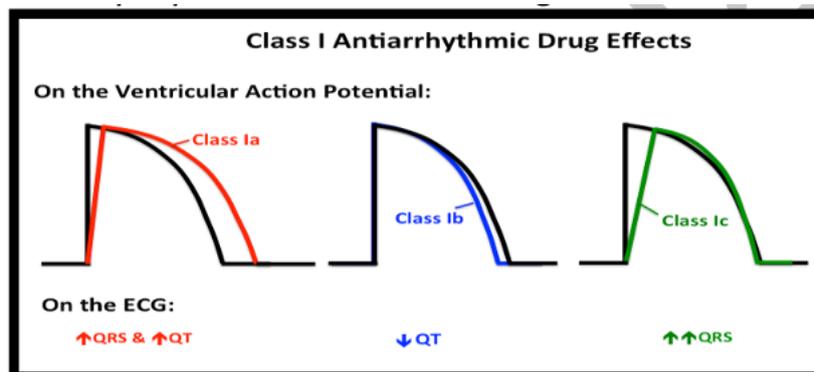


Figure 3: Class I antiarrhythmic drug effects on the action potential of a cardiac myocyte are summarised in figure 3.

CLASS II: ANTIARRHYTHMIC DRUGS

- Class II agents are β -adrenergic antagonists, or β -blockers. These drugs diminish phase 4 depolarization and, thus, depress automaticity, prolong AV conduction, and decrease 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 re-entrant tachycardia. In addition, β -blockers prevent life-threatening ventricular arrhythmias following a myocardial infarction.
- Metoprolol is the β -blocker most widely used in the treatment of cardiac arrhythmias. Compared to nonselective β -blockers, such as propranolol, it reduces the risk of bronchospasm.

- Esmolol is a very-short-acting β -blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations. It has a fast onset of action and a short half-life, making it ideal for acute situations and also limiting its adverse effect profile.
- Esmolol is rapidly metabolized by esterases in red blood cells. As such, there are no pharmacokinetic drug interactions.

CLASS III: ANTIARRHYTHMIC DRUGS

Class III agents block potassium channels and, thus, diminish the outward potassium current during repolarization of cardiac cells. These agents prolong the duration of the action potential without altering phase 0 of depolarization or the resting membrane potential. Instead, they prolong the effective refractory period, increasing refractoriness. All class III drugs have the potential to induce arrhythmias.

Amiodarone

Mechanism of action:

- Amiodarone contains iodine and is related structurally to thyroxine. It has complex effects, showing class I, II, III, and IV actions, as well as α -blocking activity.
- Its dominant effect is prolongation of the action potential duration and the refractory period by blocking K^+ channels.

Therapeutic uses:

- Amiodarone is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias.
- It has been a mainstay of therapy for the rhythm management of atrial fibrillation or flutter. Despite its adverse effect profile, amiodarone is the most commonly employed antiarrhythmic and thought to be the least proarrhythmic of the class I and III antiarrhythmic drugs.

Adverse effects

Amiodarone shows a variety of toxic effects, including pulmonary fibrosis, neuropathy, hepatotoxicity, corneal deposits, blue-gray skin discoloration, and hypo- or hyperthyroidism (why?). However, use of low doses and close monitoring reduce toxicity, while retaining clinical efficacy. Amiodarone is subject to numerous drug interactions.

- Sotalol, although a class III antiarrhythmic agent, also has potent nonselective β -blocker activity.
- It blocks a rapid outward potassium current, known as the delayed rectifier. This blockade prolongs both repolarization and duration of the action potential, thus lengthening the effective refractory period.
- Sotalol is used for maintenance of normal sinus rhythm in patients with atrial fibrillation, atrial flutter, or refractory paroxysmal supraventricular tachycardia and in the treatment of ventricular arrhythmias.
- Since sotalol has β -blocking properties, it is commonly used for these indications in patients with left ventricular hypertrophy or atherosclerotic heart disease.
- This drug can cause the typical adverse effects associated with β -blockers but has a low rate of adverse effects when compared to other antiarrhythmic agents.

CLASS IV: ANTIARRHYTHMIC DRUGS

- Class IV drugs are the nondihydropyridine calcium channel blockers verapamil and diltiazem. Although voltage-sensitive calcium channels occur in many different tissues, the major effect of calcium channel blockers is on vascular smooth muscle and the heart.
- Verapamil shows greater action on the heart than on vascular smooth muscle, and diltiazem is intermediate in its actions.
- In the heart, verapamil and diltiazem bind to open depolarized voltage sensitive channels, thus decreasing the inward current carried by calcium. They prevent repolarization until the drug dissociates from the channel, resulting in a decreased rate of phase 4 spontaneous depolarization.
- They also slow conduction in tissues that are dependent on calcium currents, such as the AV and SA nodes. These agents 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.

Digoxin

Digoxin inhibits the Na⁺/K⁺-ATPase pump, ultimately shortening 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 ventricular response rate in atrial fibrillation and flutter. At toxic concentrations, digoxin causes ectopic ventricular beats that may result in VT and fibrillation. Magnesium sulfate

- Magnesium is necessary for the transport of sodium, calcium, and potassium across cell membranes.
- It slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue.
- Intravenous magnesium sulfate is the salt used to treat arrhythmias, as oral magnesium is not effective in the setting of arrhythmia.
- Most notably, magnesium is the drug of choice for treating the potentially fatal arrhythmia torsades de pointes and digoxin-induced arrhythmias.

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