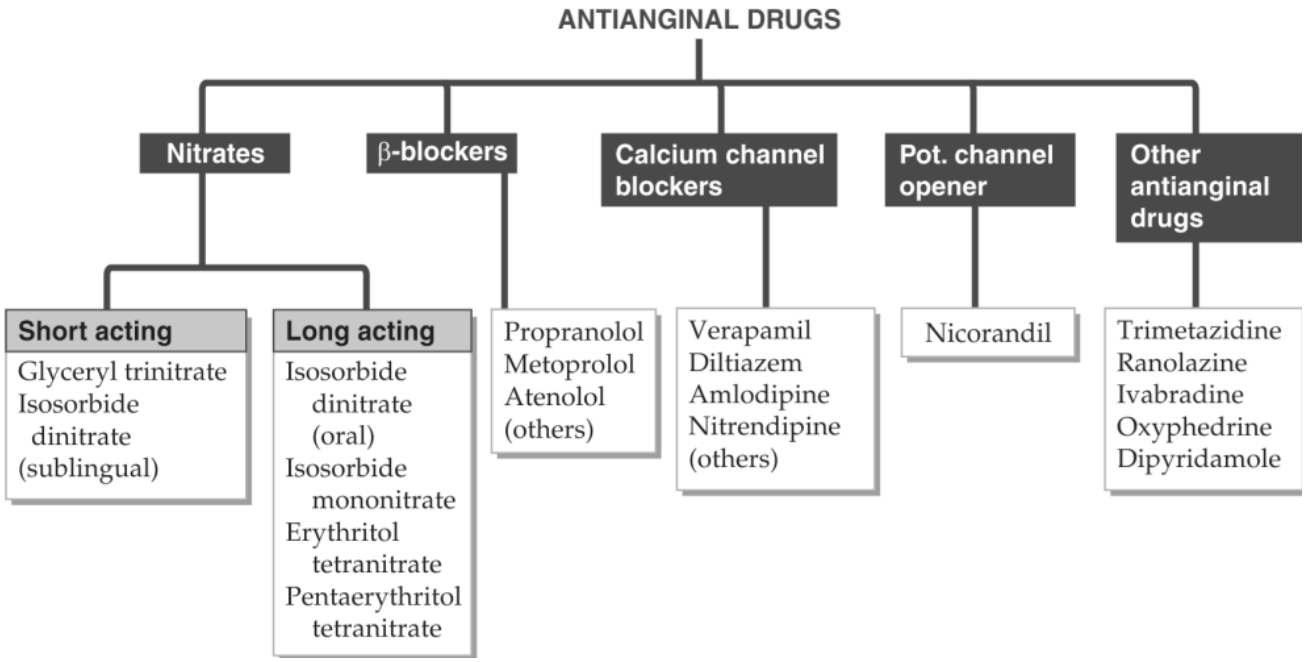
Angina and Antianginals

Angina occurs when the oxygen supply to the myocardium is insufficient for its needs. Oxygen demand of the heart is increased by increase in heart rate, contractility and heart size. Increase in myocardial fibre tension and ventricular pressure also increases oxygen requirement. Increase in end diastolic pressure (more blood in left ventricle at the end of diastole) increases the duration of systole and heart spends less time in the diastole. This may further increase the chances of anginal attacks because coronary flow occurs mainly during diastole. The pain has a characteristic distribution in the chest, arm and neck. Three kinds of angina are recognised clinically: stable, unstable and variant of Prinzmetal. Stable angina is predictable chest pain on exertion. It is produced by an increased demand on the heart. Unstable angina is characterised by pain that occurs with less and less exertion, culminating in pain at rest. Unstable angina is characterised by pain that occurs with less and less exertion, culminating in pain at rest.



Beneficial effect of nitrates in classical angina is through the reduction of preload that leads to less end diastolic pressure. Beta blockers and calcium channel blockers act by decreasing the heart rate and contractility. Recently a new strategy developed for use in angina is to make efficient utilization of substrates by the heart.

NITRATES: Large oral doses of organic nitrates decrease the frequency of anginal attacks and increase the exercise tolerance. Glyceryl trinitrate (nitroglycerine), isosorbide dinitrate (IDN), isosorbide mononitrate (IMN), erythrityl trinitrate, pentaerythritol tetranitrate and amyl nitrite are important compounds in this category.

These drugs act by releasing NO, which increase cGMP and results in venodilation. At high doses arteriolar dilation can also occur. The enzyme responsible for releasing NO from the nitrates is present mainly in the veins (therefore selective venodilator action). Venodilation results in peripheral pooling of the blood and consequently decrease in preload and end diastolic pressure. This is the main action of nitrates responsible for relief in classical angina. Nitrates also cause favourable redistribution of blood flow to the ischemic area (total coronary flow is not increased) by dilation of large epicardial coronary arteries. Because small vessels in the ischemic area are already maximal dilated (ischemia is a powerful vasodilator), blood flow to this area is selectively increased on dilation of large vessels and collaterals. Coronary vasodilatory action is mainly responsible for the therapeutic benefit of nitrates in variant/ prinzmetal angina (vasospasm is the main factor)

Nitroglycerine (NTG) is the drug of choice in all types of angina. The patient is advised to carry the tablets, and to put one sublingually as soon as precognitive symptoms develop. Patient is advised to use NTG while sitting, to avoid possible fainting. If symptoms are not relieved immediately, additional tablets may be used at 5 minute intervals, but not more than three tablets should be used in a 15 minute interval. NTG or isosorbide dinitrate, used sublingually 10-15 minutes before a period of increased activity such as walking, climbing or sexual intercourse, can frequently prevent the attack. This is the preferred method of using these drugs for prophylaxis. The acute prophylactic effect of sublingual NTG and isosorbide dinitrate persists for about 30 minutes and 2 hours respectively. Longer prophylactic effect (upto 4 hours) is obtained with NTG cutaneous ointment as NTG is absorbed slowly and bypasses the liver.

Like other vasodilators; tachycardia, flushing and headache are the major Adverse effects of Nitrates. Another problem with nitrate use is the development of tolerance on chronic use (not seen with sublingual use) requiring at least 8 hours of drug free period per day.

Molsidomine is an emerging agent in this category to which tolerance does not develop.

Phosphodiesterase inhibitors like sildenafil should never be prescribed with nitrates. Cyclic GMP is increased by nitrates and its breakdown is prevented by the inhibition of phosphodiesterase, resulting in profound hypotension (due to excess cGMP) and the risk of death.

β BLOCKERS: All beta blockers seem to be equally effective and reasonably safe as anti- anginal drugs. They are the drugs of choice for chronic prophylaxis of angina of effort. They can be combined, if necessary, with nitrates for this purpose. They are particularly preferred for the treatment of asymptomatic (silent) myocardiac ischemia. Generally, propranolol is used as starting drug with smaller dose (10 mg 3-4 times a day) and is gradually increased by 20-30 mg once in 3-4 days. The average, effective, daily dose of propranolol is about 100-200 mg. Alternatively, a selective beta blocker such as metoprolol (50-100 mg twice a day) or atenolol (50-100 mg once a day) can be used. β blockers are NOT particularly effective against angina at rest or on minimal exercise since their beneficial effect in the absence of sympathetic overactivity is small.

• Calcium channel blockers (CCBs): Variant angina is generally relieved rapidly by NTG. CCB are to be preferred for its prophylaxis. In patients with angina of effort, these drugs appear to be as effective as beta-blockers as prophylactics but they are less well tolerated. Further, they do not improve life expectancy after MI. They are mainly used in patients not responding to a combination of beta blockers and nitrates; wherein dihydropyridines can be combined with beta blocker. They can be used in patients with COPD, asthma and AV conduction disturbances.

Verapamil can be used instead of a beta blocker to control tachycardia in thyrotoxic patients with asthma. In patients with stable angina, the dose of nifedipine needs to be titrated very finely. If a patient benefits from 10 mg tid, he is likely to deteriorate on a higher dose. Calcium channel blockers have no beneficial effect, and may even be detrimental, in acute MI.

• Combination of a beta blocker and a CCB is additive but not synergistic. Verapamil should not be combined with β-blockers. Diltiazem may be combined with β-blockers only in patients with normal cardiac function and without conduction defects. Nifedipine or amlodipine and betablockers have complimentary actions on the coronary blood supply and myocardial oxygen demand. The former dilate the coronaries and decrease the BP whereas the latter slow the heart rate and reduce the myocardial contractility. The second generation dihydropyridines (e.g. amlodipine) are particularly useful in patients with angina associated with hypertension.