Drugs affecting the Cardiovascular system

(Antianginal Drugs)

Atherosclerotic disease of the coronary arteries, also known as coronary artery disease (CAD) or ischemic heart disease (IHD), is the most common cause of mortality worldwide. Atherosclerotic lesions in coronary arteries can obstruct blood flow (Figure1), leading to an imbalance in myocardial oxygen supply and demand that presents as stable angina or an acute coronary syndrome such as myocardial infarction (MI) or unstable angina.

Spasms of vascular smooth muscle may also impede cardiac blood flow, reducing perfusion and causing ischemia and angina pain.

Typical angina pectoris is a characteristic sudden, severe, crushing chest pain that may radiate to the neck, jaw, back, and arms.

All patients with IHD and angina should receive guideline-directed medical therapy with emphasis on lifestyle modifications (smoking cessation) and management of modifiable risk factors (such as hypertension and diabetes) to reduce cardiovascular morbidity and mortality.

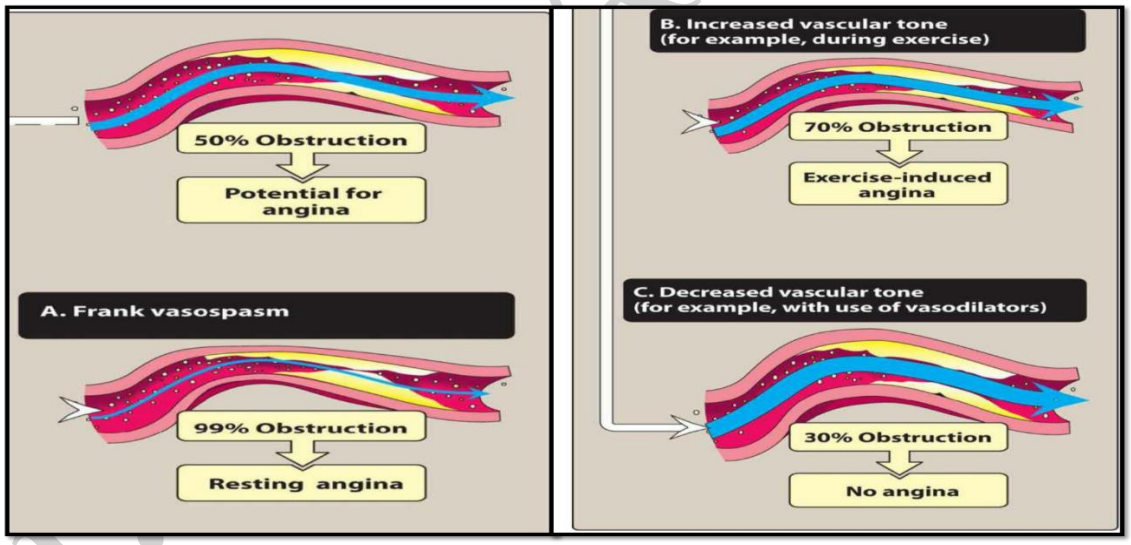

Figure 1: Blood flow in a coronary artery partially blocked with atherosclerotic plaques.

Types of Angina

Angina pectoris has three patterns: 1) stable, effort-induced, classic, or typical angina; 2) unstable angina; and 3)Prinzmetal, variant, vasospastic, or rest angina.

They are caused by varying combinations of increased myocardial oxygen demand and decreased myocardial perfusion.

A- Stable angina, effort-induced angina, classic or typical angina

Classic or typical angina pectoris is the most common form of angina. It is usually characterised by a short-lasting burning, heavy, or squeezing feeling in the chest.

Some ischemic episodes may present ''atypically''—with extreme fatigue, nausea, or diaphoresis—while others may not be associated with any symptoms (silent angina). Atypical presentations are more common in women, diabetic patients, and the elderly.

Classic angina is caused by

1- The reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by atherosclerosis.
2- Increased myocardial oxygen demand, such as that produced by physical activity, emotional stress or excitement, or any other cause of increased cardiac workload, may induce ischemia.

Typical angina pectoris is promptly relieved by rest or nitroglycerin. **When the pattern of chest pain and the amount of effort needed to trigger the chest pain does not vary over time, the angina is named "stable angina."**

B. Unstable angina

Unstable angina is chest pain that occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort. Any episode of rest angina longer than 20 minutes, any new-onset angina, any increasing (crescendo) angina, or even sudden development of shortness of breath is suggestive of unstable angina.

The symptoms are not relieved by rest or nitroglycerin. Unstable angina is a form of acute coronary syndrome and requires hospital admission and more aggressive therapy to prevent progression to MI and death.

C. Prinzmetal, variant, vasospastic, or rest angina

Prinzmetal angina is an uncommon pattern of episodic angina that occurs at rest and is due to decreased blood flow to the heart muscle caused by spasm of the coronary arteries. Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure. Prinzmetal angina generally responds promptly to coronary vasodilators, such as nitroglycerin and calcium channel blockers.

Acute coronary syndrome

Acute coronary syndrome is an emergency that commonly results from rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery. If the thrombus occludes most of the blood vessel, and, if the occlusion is untreated, necrosis of the cardiac muscle may ensue.

MI (necrosis) is typified by increases in the serum levels of biomarkers such as troponins and creatine kinase. The acute coronary syndrome may present as ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction (Figure 2), or as unstable angina. [Note: In unstable angina, increases in biomarkers of myocardial necrosis are not present.]

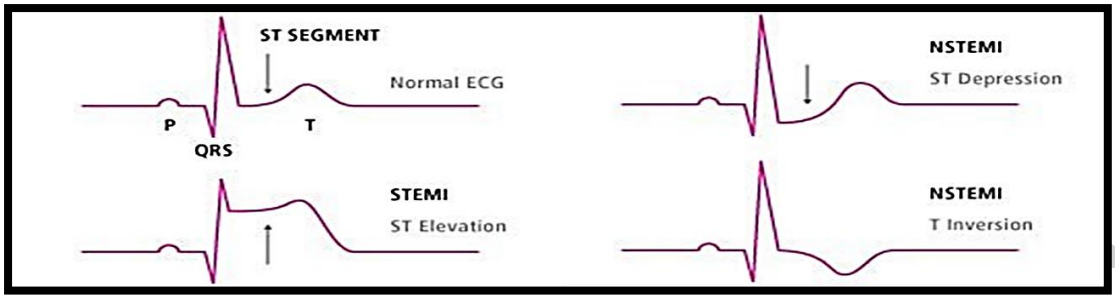

Figure 2: The differences between ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction.

Treatment Strategies

Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina: β-blockers, calcium channel blockers, organic nitrates, and the sodium channel–blocking drug, ranolazine.

These agents help to balance the cardiac oxygen supply and demand equation by affecting blood pressure, venous return, heart rate, and contractility.

Figure 3 summarises the treatment of angina in patients with concomitant diseases, and figure 4 provides a treatment algorithm for patients with stable angina.

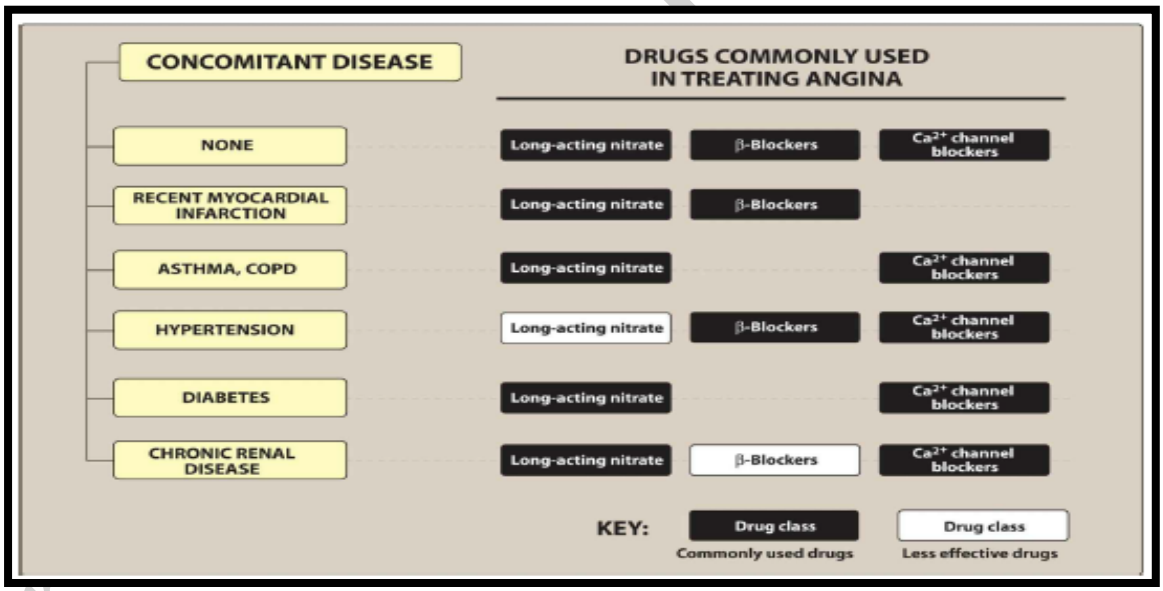

Figure 3: Treatment of angina in patients with concomitant diseases. COPD = chronic obstructive pulmonary disease.

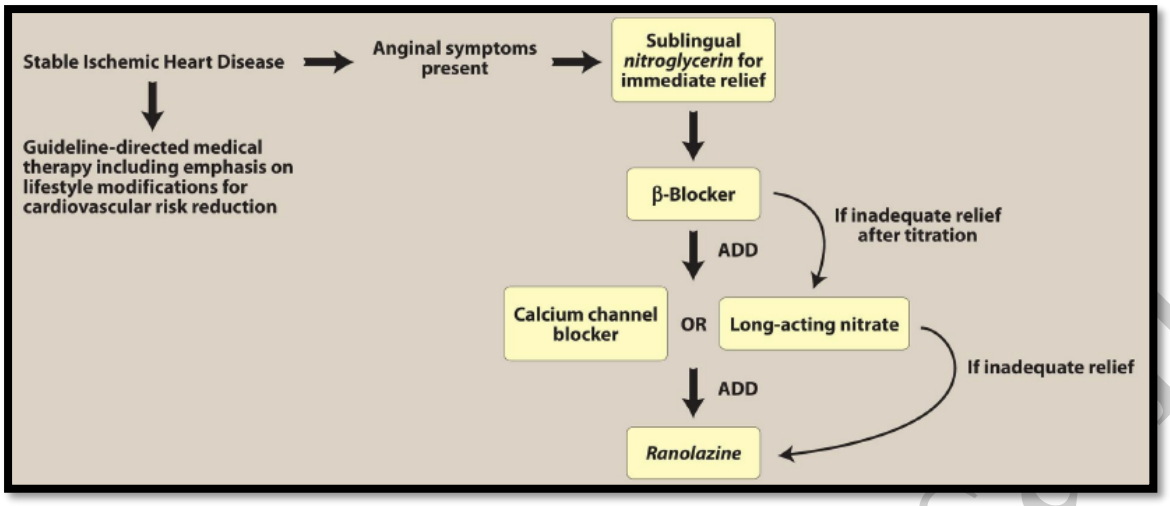

Figure 4: Treatment algorithm for improving symptoms in patients with stable angina.

Antianginal drugs mainly consist of:

1- β-Adrenergic Blockers

- **Action:** The β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking β1 receptors, resulting in decreased heart rate, contractility, cardiac output, and blood pressure. These agents reduce myocardial oxygen demand during exertion and at rest. As such, they can reduce both the frequency and severity of angina attacks.
- **Uses:**
  - β- Blockers can be used to increase exercise duration and tolerance in patients with effort-induced angina.
  - β-Blockers are recommended as initial antianginal therapy in all patients unless contraindicated. [Note: The exception to this rule is vasospastic angina, in which β-blockers are ineffective and may actually worsen symptoms.] β-Blockers reduce the risk of death and MI in patients who have had a prior MI and also improve mortality in patients with heart failure with reduced ejection fraction.
- Agents with intrinsic sympathomimetic activity (ISA) such as pindolol should be avoided in patients with angina and those with a history of MI.
- Propranolol is the prototype for this class of compounds, but it is not cardioselective. Thus, other β-blockers, such as metoprolol and atenolol, are preferred. [Note: All β-blockers are nonselective at high doses and can inhibit β2 receptors.]
- **Contraindications:**
  - β-Blockers should be avoided in patients with severe bradycardia; however, they can be used in patients with diabetes, peripheral vascular disease, and chronic obstructive pulmonary disease, as long as they are monitored closely.
  - Nonselective β- blockers should be avoided in patients with asthma.

- It is important not to discontinue β-blocker therapy abruptly. The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, MI, and hypertension.

Calcium Channel Blockers

❖ **Action:**

- Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarisation that hypoxia produces. In turn, this promotes the activity of several ATP-consuming enzymes, thereby depleting energy stores and worsening the ischemia. The calcium channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds.
- All calcium channel blockers are, therefore, arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance. These agents primarily affect the resistance of peripheral and coronary arteriolar smooth muscle.

❖ **Uses:**

- In the treatment of effort-induced angina, calcium channel blockers reduce myocardial oxygen consumption by decreasing vascular resistance, thereby decreasing afterload.
- On the other hand, their efficacy in vasospastic angina is due to relaxation of the coronary arteries. [Note: Verapamil mainly affects the myocardium, whereas amlodipine exerts a greater effect on smooth muscle in the peripheral vasculature. Diltiazem is intermediate in its actions.]
- All calcium channel blockers lower blood pressure.

❖ **Dihydropyridine calcium channel blockers**

- Amlodipine, an oral dihydropyridine, has minimal effect on cardiac conduction and functions mainly as an arteriolar vasodilator. The vasodilatory effect of amlodipine is useful in the treatment of variant angina caused by spontaneous coronary spasm.
- Nifedipine is another agent in this class; it is usually administered as an extended-release oral formulation.
- Short-acting dihydropyridines should be avoided in CAD because of evidence of increased mortality after an MI and an increase in acute MI in hypertensive patients.

❖ **Nondihydropyridine calcium channel blockers**

- Verapamil slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand. Verapamil has greater negative inotropic effects than amlodipine, but it is a weaker vasodilator.

- Verapamil is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities.
- Diltiazem also slows AV conduction, decreases the rate of firing of the sinus node pacemaker and is also a coronary artery vasodilator.
- Diltiazem can relieve coronary artery spasm and is particularly useful in patients with variant angina.
- Nondihydropyridine calcium channel blockers can worsen heart failure due to their negative inotropic effect, and their use should be avoided in this population.

Organic Nitrates

These compounds cause a reduction in myocardial oxygen demand, followed by relief of symptoms. They are effective in stable, unstable, and variant angina.

Mechanism of action

Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which in turn activates guanylate cyclase and increases synthesis of cyclic guanosine monophosphate (cGMP). Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation (Figure 5).

Nitrates such as nitroglycerin cause dilation of the large veins, which reduces preload (venous return to the heart) and, therefore, reduces the work of the heart. Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart muscle.

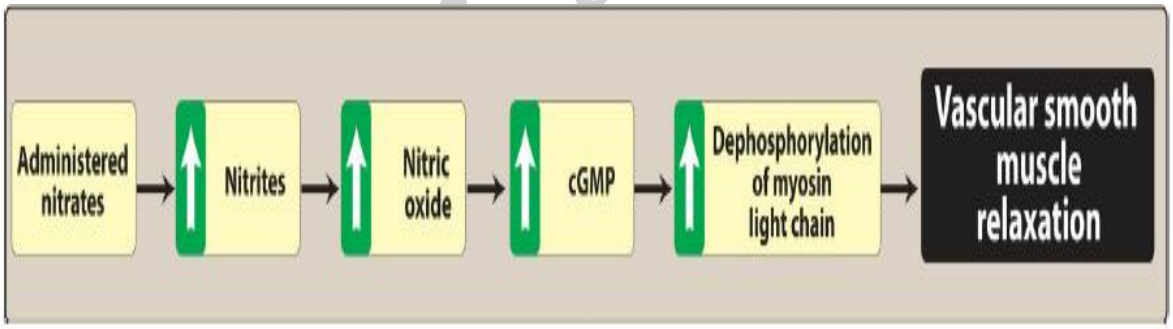

Figure 5: Effects of nitrates and nitrites on smooth muscle. cGMP = cyclic guanosine 3',5'-monophosphate.

Pharmacokinetics

- ❖ Nitrates differ in their onset of action and rate of elimination. The onset of action varies from 1 minute for nitroglycerin to 30 minutes for isosorbide mononitrate.
- ❖ Sublingual nitroglycerin, available in tablet or spray formulation, is the drug of choice for prompt relief of an angina attack precipitated by exercise or emotional stress.
- ❖ All patients should have nitroglycerin on hand to treat acute angina attacks.

- Significant first-pass metabolism of nitroglycerin occurs in the liver. Therefore, it is commonly administered via the sublingual or transdermal route (patch or ointment), thereby avoiding the hepatic first-pass effect.
- Isosorbide mononitrate owes its improved bioavailability and long duration of action to its stability against hepatic breakdown. Oral isosorbide dinitrate undergoes denitration to two mononitrates, both of which possess antianginal activity.

Adverse effects

- Headache is the most common adverse effect of nitrates. High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia.
- Phosphodiesterase type 5 inhibitors such as sildenafil potentiate the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is contraindicated.
- Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitised to vasodilation.
- Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug. The nitrate free interval of 10 to 12 hours is usually taken at night when myocardial oxygen demand is decreased. However, variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate free interval in patients with variant angina should occur in the late afternoon.
- Nitroglycerin patches are worn for 12 hours and then removed for 12 hours to provide the nitrate-free interval.

Sodium Channel Blocker

- Ranolazine improving the oxygen supply by reducing the intracellular sodium and calcium overload, thereby improving diastolic function.
- It has antianginal as well as antiarrhythmic properties. It is most often used in patients who have failed other antianginal therapies. The antianginal effects of ranolazine are considerably less in women than in men. The reason for this difference in effect is unknown.
- It can prolong the QT interval and should be avoided with other drugs that cause QT prolongation.

Figure 6 provides a summary of characteristics of the antianginal drugs.

DRUG CLASS	COMMON ADVERSE EFFECTS	DRUG INTERACTIONS	NOTES
β-Blockers *atenolol* *metoprolol* *propranolol*	Bradycardia, worsening peripheral vascular disease, fatigue, sleep disturbance, depression, blunt hypoglycemia awareness, inhibit β_2-mediated bronchodilation in asthmatics	β_2 Agonists (blunted effect); non-dihydropyridine calcium channel blockers (additive effects)	β_1-Selective agents preferred (*atenolol, metoprolol*). Avoid agents with ISA for angina therapy (*pindolol*).
Dihydropyridine calcium channel blockers *amlodipine* *felodipine* *nifedipine*	Peripheral edema, headache, flushing, rebound tachycardia (immediate-release formulations), hypotension	CYP 3A4 substrates (will increase drug concentrations)	Avoid short-acting agents as they can worsen angina (may use extended-release formulations)
Nondihydropyridine calcium channel blockers *diltiazem* *verapamil*	Bradycardia, constipation, heart failure exacerbations, gingival hyperplasia (*verapamil*), edema (*diltiazem*)	CYP 3A4 substrates (will increase drug concentrations); increase *digoxin* levels; β-blockers and other drugs affecting AV node conduction (additive effects)	Avoid in patients with heart failure Adjust dose of both agents in patients with hepatic dysfunction
Organic nitrates *isosorbide dinitrate* *isosorbide mononitrate* *nitroglycerin*	Headache, hypotension, flushing, tachycardia	Contraindicated with PDE5 inhibitors (*sildenafil* and others)	Ensure nitrate-free interval to prevent tolerance
Sodium-channel inhibitor *ranolazine*	Constipation, headache, edema, dizziness, QT interval prolongation	Avoid use with CYP 3A4 inducers (*phenytoin, carbamazepine, St. John's wort*) and strong inhibitors (*clarithromycin*, azole antifungals) and agents that prolong QT interval (*citalopram, quetiapine*, others)	No effect on hemodynamic parameters

Figure 6: A summary of characteristics of the antianginal drugs.