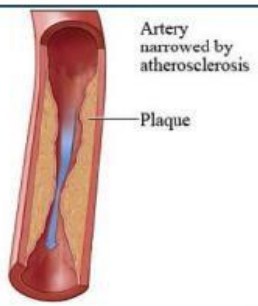
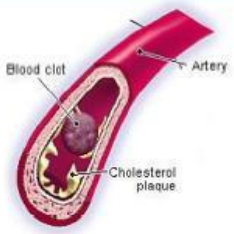
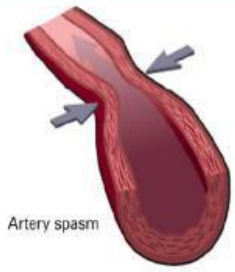
Antianginal Drugs

- Angina: is a syndrome characterized by squeezing chest pain due to transient myocardial ischemia that results from an imbalance between myocardial oxygen demand (consumption) and oxygen supply.

The cause is the narrowing of coronary arteries due to spontaneous spasm or atheromatous plaque that impairs endothelial function and reduces the release of nitric oxide (NO), the main physiological vasodilator normally produced by endothelial cells.

Types of angina pectoris:

	Stable Angina	Unstable Angina	Variant Angina
Other names	- Classical Angina - Typical Angina - Exertional Angina - Effort Angina	- Crescendo Angina - Preinfarction Angina	- Vasospastic Angina - Prinzmetal's Angina - Angina inversa
Cause	- Coronary atherosclerotic - Coronary heart disease	- Small blood clot in artery - Or coronary vasospasm - Or atherosclerotic plaque	- Coronary vasospasm
			
Distribution	- Most common	- Second most common	- Rare
Occurs	- Exertion - Emotion - Exposure to cold weather - Heavy meals	- At rest or minimal exertion	- At rest between midnight and early morning
Relief	- Decreases at rest - Relief by medicine	- Not relieved by rest or medicine	- Relieved by medicine

N.B:

- **Unstable Angina** :
  - This is a dangerous condition that requires emergency treatment.
  - **Myocardial infarction** (Heart attack) may occur in 10-20% of patients.

Classification of antianginal drugs

1. **Nitrates:** Nitroglycerin (glyceryl trinitrate), isosorbide dinitrate, isosorbide mononitrate, erythrityl tetranitrate.

2. **B_Adrenergic blockers:** Metoprolol, Atenolol, Propranolol. MAP

3. **Calcium channel blockers (CCBs):** Verapamil, diltiazem
4. **Potassium channel opener:** Nicorandil.

5. **Others***: Antiplatelet agents, (low-dose aspirin, clopidogrel), Statins, Trimetazidine, Ranolazine

✓ Drugs aim to: decrease the myocardial O2 consumption (demand) and / or improve the myocardial O2 supply.

Anti-anginal Drugs

1. Organic Nitrate

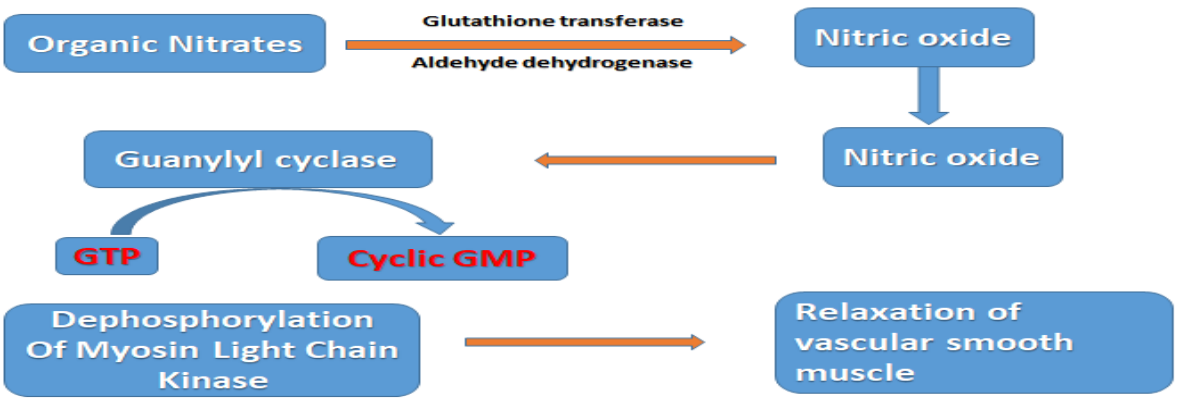
- Organic nitrates are prodrugs—they release nitric oxide (NO). Nitrates are mainly venodilators, which also cause arteriolar dilatation, reducing both preload and afterload.

- Nitrates differ in their onset of action and rate of elimination

Mechanism of action:

- They relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide **(NO)**. This process requires a presence of **free SH groups**.
- Nitric oxide activates the soluble guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP) a second messenger which alters Ca^{+2} fluxes in the cells and decreases intracellular Ca^{+2} level resulting in **vascular smooth muscle relaxation and vasodilatation.**

❖ **SH group** are required for formation of **NO**



Pharmacological Effects:

- They mainly dilate large veins, which results in pooling of blood in the veins.
- This reduces venous return and left ventricular filling pressure. The resultant decrease in the ventricular wall tension (preload) **reduces the cardiac work** and **decreases the myocardial oxygen consumption**.
- They dilate coronary arteries, relax coronary spasm or vasoconstriction, and improve myocardial perfusion (this action cause favorable redistribution of blood flow to ischemic areas ⟹ increased O_2 delivery to the ischemic area).

Venous dilation ⟹ decreases preload (venous return to the heart)

Arteriolar dilation ⟹ decreases afterload

- Other vascular beds, Nitrates can cause dilation of Cutaneous blood vessels giving rise to **flushing** and Meningeal vessels dilation which causes **throbbing headache**.
- **Smooth muscles relaxation** of Gall bladder, biliary ducts, bronchi, GIT.

So, the relief of chest pain by nitrates does not prove the diagnosis of angina pectoris because they can relax smooth muscle in the bronchi, esophagus, gall bladder and biliary tract and can relieve chest pain due to spasm of smooth muscle of these organs.

Pharmacokinetics

Organic nitrates are readily absorbed through the buccal mucous membrane, the skin and gastrointestinal (GI) tract. All nitrates **except** isosorbide mononitrate undergo extensive first-pass metabolism; hence,
oral bioavailability of nitrates is very low. Sublingual route produces rapid onset (2–5 min) but short duration of action. Absorption through skin is slow; hence, transdermal route is used for a prolonged effect. The metabolites are excreted mainly in urine as glucuronide derivatives.

Nitrates differ in their onset of action and rate of elimination
Nitroglycerine is the prototype of the group and its well absorbed from the mucosal surface of the mouth .and when administered **sublingually** produces its effect within a few minutes, so the sublingual route is preferred to terminate **acute Anginal attack;** by this route, the effective duration of action is short (about 30 minutes)

Nitroglycerine is well absorbed through the skin, and a more sustained (prolonged) effect can be achieved by applying it as a transdermal patch.

Isosorbide mononitrate has similar pharmacological actions but longer duration, slower onset, less hepatic first pass metabolism, and more reliable systemic bioavailability than glyceryl trinitrate.

Isosorbide mononitrate is taken **orally** for **prophylaxis in chronic angina**

Side Effects

are direct results of their vasodilating actions.

1-Postural hypotension, dizziness, fainting and syncope. (The patient should remain supine; if symptoms are severe, he should also spit out or swallow the remainder of the tablet.)

2 -Reflex tachycardia

3- facial flushing

4 -Throbbing headache :Tolerant headache develops quickly but re-occurs after a brief nitrate-free period.

5-Over doses can cause methemoglobinemia due to the oxidation of iron in haemoglobin to ferric ions.

TOLERANCE (tachyphylaxis):

- Continuous administration of nitrates results in diminished vasodilatation and antianginal effect, Possibly because of the **depletion of free SH groups** in the vascular smooth muscle cells.
- It does not occur with short-acting preparations as sublingual glyceryl trinitrate but mainly occurs with long-acting preparations as **isosorbide mononitrate** or when glyceryl trinitrate is administered by prolonged I.V infusion.
- Tolerance develops quickly (within 24 hours) and wears off quickly after a brief nitrate-free period and can be prevented by providing a **daily nitrate-free interval** to restore sensitivity to the drug.
- This interval is typically **8-10 hours at night**. I.e. skin patches are removed at night and worn in the morning or isosorbide mononitrate is administered at lunch and in the morning / to allow nitrate-free period at night.

2. Beta blockers:

FDA Approved Beta Blockers for Angina

- Atenolol (Tenormin)

- Metoprolol (Toprol XL, Lopressor)
- Propranolol (Inderal LA)
- Beta-blockers decrease myocardial O2 requirement at rest and during exercise because they decrease the heart rate, blood pressure and myocardial contractility.
- They are useful in **chronic prophylaxis** for **exercise-induced angina**.
- Beta-blockers that possess intrinsic sympathomimetic activity such as pindolol are less effective in angina.
- Beta-blockers should not discontinue abruptly, but the dose should be gradually tapered over **5-10 days** to avoid the risk of rebound angina.
- They are contraindicated in angina due to coronary artery spasms (variant angina).
  Q: why are beta blockers contraindicated in variant angina?
- Variant angina is occurred due to coronary spasm
- Coronary arteries contains both **α** and **β** receptors ⟹ Blockade of beta receptors causes unopposed alpha action and leads to vasoconstriction and aggravation of variant angina.

β-blocker ONLY used for Stable & unstable Angina.

3. Calcium Channel Blockers:

FDA Approved Calcium Channel Blockers for Angina:

- ✓ Verapamil
- ✓ Diltiazem
- ✓ Amlodipine (useful in the treatment of variant angina)
- ✓ Nifedipine (useful in the treatment of variant angina)

Mechanisms of Action

1. Block calcium influx through voltage-gated L-type Ca channels in both cardiac & vascular smooth muscle
2. Reduced oxygen consumption (O2 demand) due to:

↓heart rate ------ ↓contractility ------ ↓afterload (↓TPR & BP) - with little effect on venous resistance

3. Increased coronary blood flow (especially useful for vasospastic angina)

Side effects

1. headache, flushing, dizziness, peripheral (ankle) oedema, Constipation
2. Nifedipine can cause hypotension with reflex tachycardia and palpitation, diltiazem and verapamil can cause bradycardia.

4.Nicorandil

- is an arterial and venodilator, reduces preload and after load so reduce cardiac work and O_2 consumption.
- It liberates NO and increases the level of cGMP which causes vasodilatation. It also activates and opens K+ channels in vascular smooth muscle cell's membrane to allow K+ efflux (exit) which leads to hyperpolarization that reduces Ca^{+2} entry and induces vasodilatation
- It is administered orally and it is an alternative to nitrates in patients who develop tolerance, or to other classes when these are contraindicated.
- side effects are headache, hypotension, palpitation, flushing, nausea and vomiting

Other Drugs

- Antiplatelet agents like **aspirin** (low dose 81–325 mg daily) or clopidogrel are used.
- Ranolazine and trimetazidine are used along with conventional antianginal drugs instable angina.

Key Points for Dentists

- For an acute attack of angina, nitroglycerin is commonly administered sublingually with an initial dose of 0.5 mg that usually relieves pain in 2–3 min.

- Patient is advised to spit out the tablet as soon as the pain is relieved to avoid the side effects (hypotension and headache).

- If the pain is not relieved, the tablet can be repeated after 5 min; but not more than 3 tablets in 15 min.