ANTI-ANGINAL DRUGS

Anti-anginal: Vasodilators: Amyl nitrite, Nitroglycerin*, Pentaerythritol tetranitrate, Isosorbide dinitrite*, Dipyridamole. Calcium channel blockers: Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine.

DRUGS ACTING ON CARDIOVASCULAR SYSTEM

The drugs acting on cardiovascular system are divided into four groups:

1. Cardiotonic drugs.
2. Anti-hypertensive drugs.
3. Anti-arrhythmic drugs
4. Anti-anginal drugs.

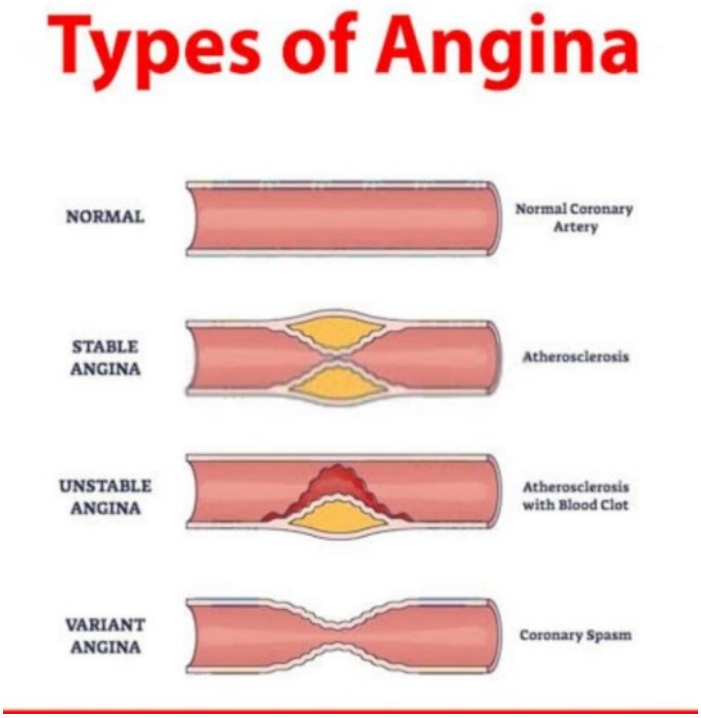
- The word angina (meaning in Greek: to choke) is used to describe the pain or discomfort of cardiac origin which results due to temporary ischemia of the myocardium, that is flow of blood is inadequate to maintain the metabolic demand of heart for oxygen and nutrients.
- The coronary circulation supplies blood to the myocardial tissue to maintain cardiac function.
- It dilates the blood vessel to provide sufficient oxygen and other nutrient and to remove metabolites.
- Angina is caused by the coronary vessel constriction which prevents this blood flow.

ANTIANGINAL DRUGS

- These are the drugs used in the treatment of angina pectoris. Angina pectoris or Angina.
- **Angina**, is severe chest pain due to ischemia (a lack of blood, hence a lack of oxygen supply) of the heart muscle, generally due to obstruction or spasm of the coronary arteries.
- Coronary artery disease, the main cause of angina, is due to atherosclerosis of the cardiac arteries.
- Major risk factors for angina include cigarette smoking, diabetes, high cholesterol, high blood pressure, sedentary lifestyle and family history of premature heart disease.
- Antianginal agents may improve angina by reducing the demand or by increasing the supply of oxygen and dilates coronary arteries and decrease after load.

TYPES OF ANGINA PECTORIS

There are three types:



1. Stable angina: In this type the atherosclerotic plaque and inappropriate vasoconstriction (caused by endothelial damage) reduce the blood vessel lumen diameter. Hence there is reduction of blood flow.

2. Unstable angina: In unstable angina, rapture of the plaque triggers platelet aggregation, thrombus formation, and vasoconstriction. Depending upon plaque rapture this leads to non-Q wave (non-ST elevation) or Q wave (ST elevation).

3. Variant angina: In this type atherosclerotic plaques are absent, and ischemia is caused by intense vasospasm. It occurs more in younger women.

CLASSIFICATION

I) Nitrites and Nitrates: eg. Amyl Nitrite, Isosorbide Dinitrate, Nitroglycerin(Glyceryl trinitrate-GTN), Erythrityl Tetranitrate, Pentaerythritol Tetranitrate,
II) B-adrenergic blocking agent: eg. Propranolol
III) Calcium channel blockers:
a) 1,4-Dihydro pyridine: eg.Nifedipine. Nimodipine, Nisoldipine, Felodipine, Benidipine, Lacidipine.
b) Phenyl alkyl amines: eg. Verapamil
c) Benzothiazepines: eg. Diltiazem.
d) Diamino propanol ether: eg. Bepridil.
IV) Cardiovascular agents: eg. Digoxin, Digitoxin, Deslanoside, Ouabain.
V) Miscellaneous agent: eg. Dipyridamole

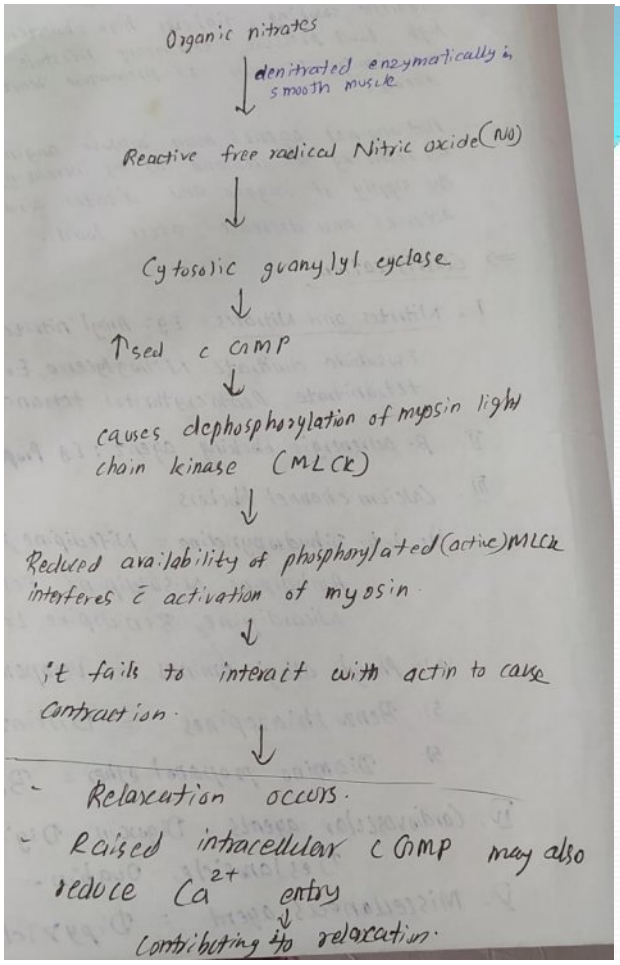
VASODILATORS

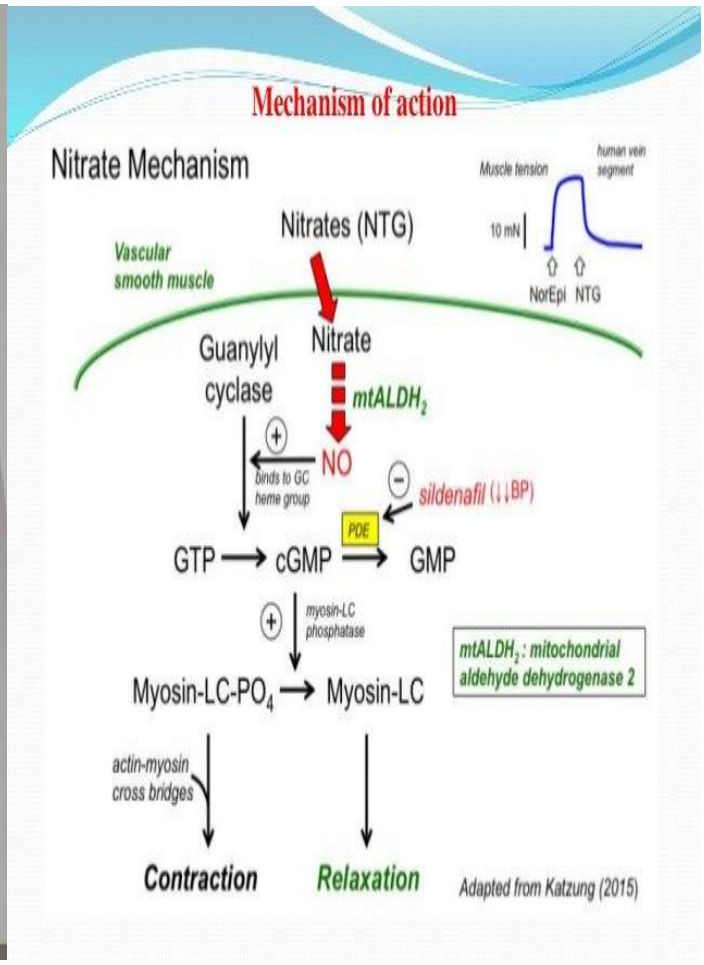
I.Nitrates

- A nitro vasodilator is a pharmaceutical agent that causes vasodilation (widening of blood vessels) by donation of nitric oxide (NO), and is mostly used for the treatment and prevention of angina pectoris.

MOA

- Within the body, organic nitrates are chemically reduced to release NO.
- NO is an endogenous signaling molecule that causes vascular smooth muscle relaxation.
- The various organic nitrates give rise to NO by different chemical and biochemical mechanisms.
- Organic nitrates have the chemical structure RNO_2.
- The nitro group is reduced to form NO in the presence of specific enzymes and extracellular and intracellular reductants (e.g. thiols).
- The NO activates guanylylcyclase. The activated guanylylcyclase increases the formation of cGMP from GTP.
- The cGMP activates myosin-LC phasphatase.
- The activated myosin-LC phasphatase causes the dephosphorylation of myosin-LC-(P) to myosin-LC.
- This relaxes the smooth muscle and causes vasodilatation.





i. Amyl nitrite or Isopentyl nitrite

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- Amyl nitrite's **antianginal action** is thought to be the result of a reduction in systemic and pulmonary arterial pressure (afterload) and decreased cardiac output because of peripheral vasodilation, rather than coronary artery dilation.
- Amyl nitrite is a source of nitric acid, which accounts for the mechanism described above.
- As an **antidote** (to cyanide poisoning), amyl nitrite promotes formation of methemoglobin, which combines with cyanide to form nontoxic cyanmethemoglobin.

Uses

- Amyl nitrite is employed medically to treat heart diseases as well as **angina**.
- Amyl nitrite is sometimes used as an **antidote** for cyanide poisoning.
- It can act as an **oxidant,** to induce the formation of methemoglobin.

ii. Isosorbide Dinitrate (ISDN)

MOA

- It relaxes the vascular smooth muscle and consequent dilatation of peripheral arteries and veins,
- especially the latter.
- Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload).
- Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and means arterial pressure.

Synthesis

Uses

- Isosorbidedinitrate (ISDN) is a medication used for **heart failure**, **esophageal spasms**, and to treat and prevent **chest pain** from not enough blood flow to the heart.
- It has been found to be particularly useful in heart failure due to systolic dysfunction together with hydralazine in black people.

iii. Nitroglycerin(Glyceryl trinitrate-GTN)

MOA

- Similar to other nitrites and organic nitrates, nitroglycerin is converted to nitric oxide (NO), an active intermediate compound which activates the enzyme guanylatecyclase.
- This stimulates the synthesis of cyclic guanosine 3',5'-monophosphate (cGMP) which then activates a series of protein kinase-dependent phosphorylations in the smooth muscle cells, eventually resulting in the dephosphorylation of the myosin light chain of the smooth muscle fiber.
- The subsequent release of calcium ions results in the relaxation of the smooth muscle cells and vasodilation.

Synthesis

Uses

- Nitroglycerin extended-release capsules are used to **prevent chest pain (angina)** in people with a certain heart condition (coronary artery disease).
- This medication belongs to a class of drugs known as nitrates.
- This drug works by relaxing and widening blood vessels so blood can flow more easily to the heart.
- It has a strong **vasodilation action**.

iv. Pentaerythritol tetranitrate (PETN)

Uses

- Like nitroglycerin (glyceryltrinitrate) and other nitrates, PETN is also used medically as a **vasodilator i**n the treatment of heart conditions.
- PETN is used prophylactically to reduce the severity and frequency of **angina pectoris**.
- These drugs work by releasing the signaling gas nitric oxide in the body.
- The heart medicine Lentonitrat is nearly pure PETN.

II. Calcium channel blockers (CCBs)

- These are medicines that are often used to treat high blood pressure.
- Most of these medicines will have names that end in "ipine".
- These are an important class of cardiovascular drugs which act by inhibiting L type voltage
- sensitive calcium channel s in smooth muscle and heart.
- There are five pharmacologically distinct subclasses of calcium channel blockers.

Mechanism of action

- Calcium is necessary for the excitation contraction coupling in both the skeletal and smooth muscle.
- A calcium channel embedded in a cell membrane.
- In the body's tissues, the concentration of calcium ions (Ca) outside cells is normally about 10000-fold higher than the concentration inside cells.
- When these cells receive a certain signal, the channels open, letting calcium rush into the cell.
- The resulting increase in intracellular calcium has different effects in different types of cells.
- Calcium channel blockers prevent or reduce the opening of these channels and thereby reduce these effects.
- **CCBs** block the **L-type voltage-gated** calcium channel.
- The L-type channel is the site of action of calcium channel blockers and reduces Ca flux through the channel.
- This reduces the availability of intracellular calcium.
- Voltage-dependent calcium channels are responsible for excitation-contraction coupling of skeletal, smooth and cardiac muscle and for regulating aldosterone and cortisol secretion in endocrine cells of the adrenal cortex.
- In the heart, they are also involved in the conduction of the pacemaker signals.
  - Potential depending channel can exists in one of the three conformations:

- Resting state- which can be stimulated by membrane depolarization
- Open state- which allows the Ca^{+} to enter
- Inactive state- when is refractory to further depolarization.
- Calcium channel blockers act by prolonging depolarization; which inhibits conduction velocity and contraction.
- As a result, calcium channel blockers are therapeutically used in angina, arrhythmiasis, hypertension and cardio vascular disorders.

Classification of Calcium Channel blockers

Class I Phenylalkylamines - Verapamil

Class II Benzothiazepines - Diltiazem

Class III Dihydropyridines

First generation - Nifedipine

Second generation - Felodipine

Third generation - Amlodipine

a.Class I Phenylalkylamines

i. Verapamil

MOA

- Verapamil inhibits voltage-dependent calcium channels.
- Specifically, its effect on L-type calcium channels in the heart causes a reduction in ionotropy and chronotropy, thus reducing heart rate and blood pressure.
- Verapamil's mechanism of effect in cluster headache is thought to be linked to its calcium-channel blocker effect, but which channel subtypes are involved is presently not known.

Uses

- Verapamil is also used **to prevent chest pain** (angina).
- It may help to increase your ability to exercise and decrease how often you may get angina attacks. Verapamil is also used to **control your heart rate** if you have a fast/irregular heartbeat (such as atrial fibrillation).

- It helps to lower the heart rate, helping you to feel more comfortable and increase your ability to exercise.

ii. Bepridil hydrochloride

Uses

- Bepridil Hydrochloride is a medicine that is used for the treatment of **Hypertension,** Atrial **fibrillation** and other conditions.

b. Class II Benzothiazepines

i. Diltiazem hydrochloride

Uses

- Diltiazem used in the treatment of **hypertension**, **angina pectoris**, and some types of **arrhythmia.**
- It **relaxes the smooth muscles** in the walls of arteries, which opens (dilates) the arteries, allows blood to flow more easily, and **lowers blood pressure**.
- It lowers blood pressure by acting on the heart itself to reduce the rate, strength, and conduction speed of each beat.

c. Class III Dihydropyridines

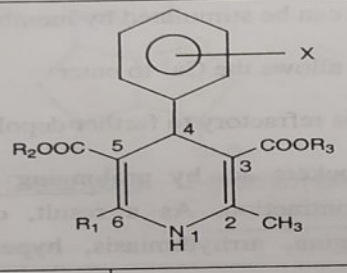
i) 1,4-Dihydro pyridine (DHP)

SAR

- A substituted **phenyl ring** substitution at **4th** position **optimizes** activity.
- Substitution at **para** or **unsubstituted phenyl** ring **decreases** the activity.
- Phenyl ring substitution (X) is important for **size** and **position** rather than for electronic nature.

- Compounds with **ortho** or **meta** substitutions possess **optimal activity**, while those which are unsubstituted or contain a para-substitution show a significant decrease in activity.
- **Electron withdrawing** ortho or meta-substituents or **electron donating** groups demonstrated **good** activity.
- The importance of the **ortho** and **meta-**substituents is to provide sufficient **bulk** to "lock" the conformation of the 1, 4-DHP such that the C4 aromatic ring is perpendicular to the 1, 4-dihydropyridine ring. This perpendicular conformation has been proposed to be essential for the activity.
- **1,4 Dihydro pyridine** ring is **essential** for activity.
- **Substitution at N1** or **oxidation** (piperidine) or **reduction** (pyridine) of the ring **decreases** or abolishes the activity.
- The **C3rd** and **C5th** position **ester** group **optimizes** activity. Any other electron withdrawing substitution results in agonist activity.
- When the ester at C_3 and C_5 are non-identical the C_4 become **chiral** and stereo selectivity is observed. **S- enantiomers** have proved to be more **effective.**
- With the exception of amlodipine, all 1, 4-DHPs have C2, and C6 methyl groups.

Table No. 13.1 Structure of 1,4 – Dihydro Pyridine Derivatives



S. No	Compounds	R_1	R_2	R_3	X
1.	Amlodipine	$-CH_2O(CH_2)_2NH_2$	$-C_2H_5$	$-CH_3$	2 -Cl
2.	Felodipine	$-CH_3$	$-C_2H_5$	$-CH_3$	2,3 - Cl_2
3.	Nifedipine	$-CH_3$	$-CH_3$	$-CH_3$	2 - NO_2
4.	Nitrendipine	$-CH_3$	$-CH_3$	$-C_2H_5$	3 - NO_2
5.	Nimodipine	$-CH_3$	$-CH_2CH_2OCH_3$	$-CH(CH_3)_2$	3 - NO_2
6.	Nisoldipine	$-CH_3$	$-CH_2CH(CH_3)_2$	$-CH_3$	2 - NO_2

i. Nifedipine

Uses

- Nifedipine, is a medication used to manage **angina**, **high blood pressure**, **Raynaud's phenomenon**, and **premature labor**.
- It is one of the treatments of choice for **Prinzmetal angina**.
- It may be used to treat severe **high blood pressure in pregnancy**.
- Its use in preterm labor may allow more time for steroids **to improve the baby's lung function** and provide time for transfer of the mother to a well qualified medical facility before delivery.

ii. Amlodipine

Uses

- Amlodipine is used in the management of **hypertension** and **coronary artery disease** in people with either **stable angina** (where chest pain occurs mostly after physical or emotional stress) or **vasospastic angina** (where it occurs in cycles) and without heart failure.
- It can be used as either monotherapy or combination therapy for the management of hypertension or coronary artery disease.

iii. Felodipine

Uses

- Felodipine is used to treat high blood pressure (**hypertension**).
- Lowering high blood pressure helps prevent **strokes**, **heart attacks**, and **kidney problems**.
- Felodipine is known as a calcium channel blocker.
- By blocking calcium, this medication relaxes and widens blood vessels so blood can flow more easily.

iv. Nicardipine

Uses

- Nicardipine is used with or without other medications to treat high blood pressure (**hypertension**).
- Lowering high blood pressure helps prevent **strokes**, **heart attacks**, and **kidney problems.**
- Nicardipine is called a calcium channel blocker.
- It works by relaxing blood vessels so blood can flow more easily.

v. Nimodipine

Uses

- Nimodipine's main use is in the prevention of **cerebral vasospasm** and **resultant ischemia**, a complication of subarachnoid hemorrhage (a form of cerebral bleed), specifically from ruptured intracranial berry aneurysms irrespective of the patient's post-ictus neurological condition.

III. Miscellaneous agent

Dipyridamole

MOA

Dipyridamole has two known effects, acting via different mechanisms of action;

- Dipyridamole inhibits the phosphodiesterase enzymes that normally break down AMP (increasing cellular cAMP levels and blocking the platelet aggregation response to ADP) and/or cGMP.
- Dipyridamole inhibits the cellular reuptake of adenosine into platelets, red blood cells, and endothelial cells, leading to increased extracellular concentrations of adenosine.

Uses

- Dipyridamole inhibits both adenosine deaminase and phosphodiesterase preventing the degradation of cAMP, an **inhibitor of platelet function**.

- This elevation in cAMP blocks the release of arachidonic acid from membrane phospholipids and **reduces thromboxane A2 activity**.
- Dipyridamole also directly stimulates the release of prostacyclin, which induces adenylatecyclase activity, thereby raising the intraplatelet concentration of cAMP and further inhibiting platele aggregation.
- Used as long acting **vasodilator.**
- Used to treat **angina pectoris.**