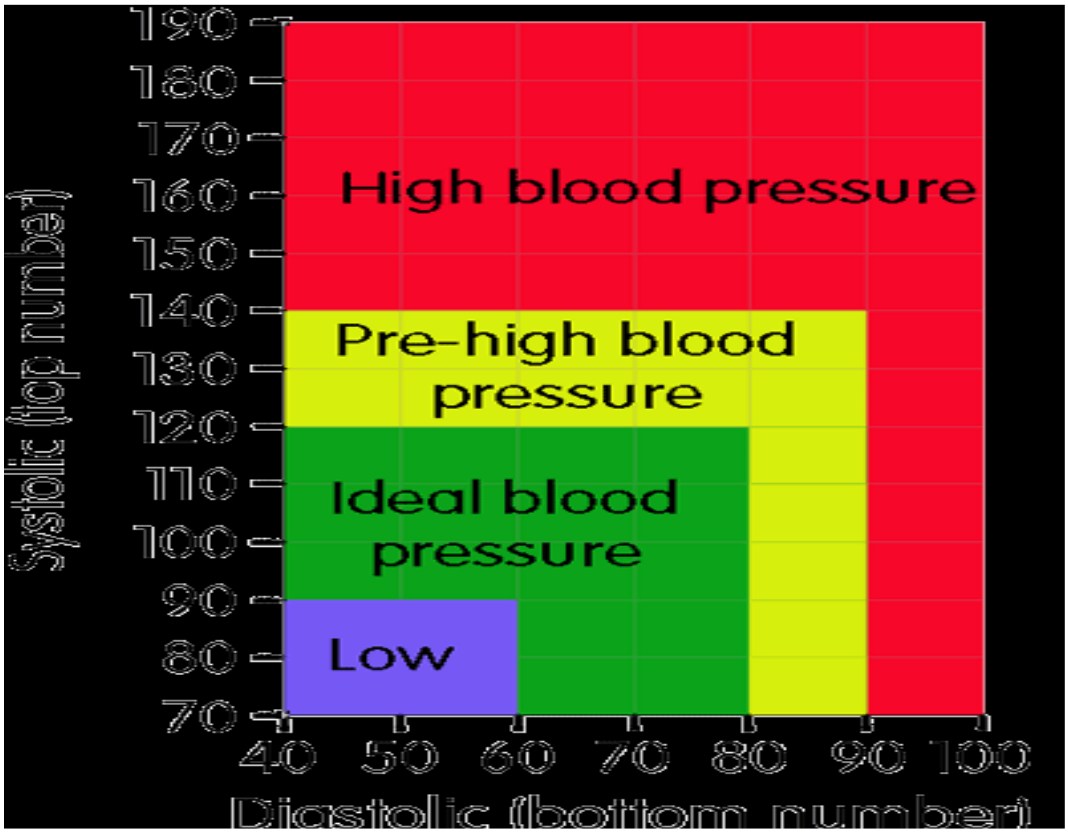
Chapter3 -Pharmacology of Drugs acting on Cardiovascular Systems

Anti- hypertensives agents: Classification and mechanism of action, Pharmacology of centrally acting drugs (Clonidine and methyldopa), Classification of vasodilators including calcium channel blockers, Pharmacology of drugs affecting Renin Angiotensin system. Anti - anginal drugs; Classification and pharmacology of anti -anginal drugs. Anti-arrhythmic drugs; Classification and mechanism of action, Pharmacology of quinidine (A proto type sodium channel blocker), Salient features of other anti-arrhythmic drugs, Drugs used for therapy of congestive cardiac failure (CCF); Classification and mechanism of action of drugs used for CCF, pharmacology of digoxin, Salient features of other drugs used in CCF. Drugs used in treatment of hyperlipidaemias; Classification and mechanism of action of anti- hyperlipidaemics, Pharmacology of atorvastatin (A proto type of HMG CoA reductase inhibitor), Salient features of other anti- hyperlipidaemic agents. **14 hours; 12-14 marks**

a)Anti- hypertensive agents: Classification and mechanism of action

Blood pressure- It is the lateral pressure exerted by the blood on its wall. Cardiac output (CO) determines the systolic BP, while peripheral resistance (PR) determines the diastolic BP. Normal BP 120/80 mmHg

Purpose of HT treatment- It is not only to lower the BP, but to protect the target organs-heart, brain, eyes, and kidneys. These organs are damaged if HT is not properly controlled.



Classification of antihypertensive drugs-
1. Centrally acting drugs - Clonidine, α methyldopa
2.Ganglion blockers- a-Competitive ganglion blockers: Trimetaphan, Tetraethylammonium (TEA), Mecamylamine, and Pempidine.
b.Non competitive ganglion blockers: Hexamethoneum
3.Adrenergic neuron blockers- Reserpine, guanethidine.
4.α blockers- α1 and α2 blockers- Phentolamine, and phenoxybenzamine.
Specific α1 blockers- Prazosin, terazosin, doxazosin.
5.β blockers- Non selective **β blockers**- Propranolol, **β1 blockers-** atenolol, metaprolol,
6. Calcium channel blockers (CCB) - Verapamil, diltiazem, nifedipine, amlodipine.
7.ACE- inhibitors- Captopril, lisinopril, enalapril, ramipril, benazepril
8.Angiotensin receptor antagonist- Saralasin, losartan, telmisertan, valasertan, candesertan.
9.Direct acting vasodilators- Hydralazine, minoxidil, Na nitropresside-
10.Aldosterone antagonist- eg-Spiranolactone
11.Diuretics- Thiazides and loop diuretics- frusemide
(First 5 classes are sympatholytics).

Mechanism of actions of antihypertensive drugs
1. Centrally acting drugs- Clonidine, α methyldopa
Clonidine- It acts on α2 receptors (auto-receptors) located in the vasomotor center of the brain. The presynaptic membranes of the adrenergic nerve endings of the vasomotor center have α2 receptors. Upon stimulation the released adrenaline/Nor-adrenaline also binds to these receptors. These receptors belong to the Gi type of G protein coupled receptors. The activation of α2 receptors causes activation of K+ channel, closure of Ca2+ channel. This leads to hyper-polarization (IPSP). This decreases the secretion of nor-adrenaline and resulting in vasodilatation (due to decreased interaction between nor-adrenaline with alpha receptors located on the vascular smooth muscles). This decreases peripheral resistance in the blood vessels and diastolic BP. The decreased sympathetic activity also decreases force of contraction of the heart and cardiac output. This decreases systolic B.P. Thus clonidine decreases both diastolic and systolic pressure.
Methyldopa –It is an antihypertensive drug and is the L-isomer of alpha-methyldopa. Its brand name is aldomet. It has a dual mechanism of action 1. It acts by inhibiting the enzyme DOPA decarboxylase (it converts L-DOPA to dopamine). This results in decreased formation of nor-adrenaline/adrenaline. This decreases B.P
2. Dopamine β-hydroxylase converts α methyl-dopa to methyl nor-adrenaline in the synaptic vesicles of the sympathetic nerves. The released methyl nor-adrenaline acts as false neurotransmitters for the alpha receptors present on the blood vessels. This interaction results in vasodilatation and decreases the BP.

2. Ganglion blockers-
a-Competitive ganglion blockers: Trimetaphan, Tetraethylammonium (TEA), Mecamylamine, and Pempidine.
b.Non competitive ganglion blockers: Hexamethoneum
Ganglionic blockers block both sympathetic and parasympathetic ganglia. These drugs are potent antihypertensive drugs but their use is limited to short term treatment of hypertension associated with dissecting aneurysm of aorta (when an artery wall in the aorta weakens, the wall abnormally expands or bulges as blood is pumped through it, causing an aortic aneurysm) and in the production of controlled hypotension during surgery.

Ganglionic blockers act by blocking the Nn receptors found in the sympathetic and parasympathetic ganglia. The acetylcholine is the agonist for the Nn receptors having both affinity and intrinsic activity. But ganglionic blockers have only affinity. They bind to the binding site located in the two alpha subunits of the Nn receptors. Due to blockage the nicotinic receptors no conformational change in the pore size in the receptors. Hence the sodium ion fails to pass through the receptors. This initiates the inhibitory post synaptic potential (IPSP) and the release of neurotransmitters (adrenaline/NA, acetylcholine) decreases. The decreased release of adrenaline/NA neurotransmitters causes antihypertensive effect.

3. Adrenergic neuron blockers- Reserpine, guanethidine

Reserpine- It is an alkaloid obtained from *Rauwolfia serpentina*. It irreversibly blocks the vesicular monoamine transporter (VMAT). The VMAT is a transport protein integrated into the membrane of synaptic vesicles of presynaptic neurons. VMAT are responsible for the uptake of cytosolic monoamines (eg dopamine, nor-adrenaline, histamine, serotonin, etc) into vesicles in monoaminergic neurons. Unprotected neurotransmitters (nor-adrenaline and dopamine) are metabolized by MAO and COMT in the cytoplasm. This leads to decreased secretion of nor-adrenaline and decreased BP. Its use is restricted in hypertension due to its depletion of neurotransmitter effect.

Guanethidine- It is an antihypertensive drug that reduces the release of nor-adrenaline. Guanethidine is transported across the sympathetic nerve membrane (re uptake mechanism) similar to nor-adrenaline. Within the nerve terminal guanethidine is concentrated in the synaptic vesicles, where it replaces the nor-adrenaline. This leads to a gradual depletion of nor-adrenaline stores in the nerve endings. This leads to a gradual depletion of norepinephrine. This inhibits the release of nor-adrenaline and decreases the BP. It is banned in most of the country. But in some countries (eg.UK), it is used for the rapid control of BP in hypertensive emergency.

4. α blockers- α1 and α2 blockers- Phentolamine, and phenoxybenzamine. They blocks both α1 and α2 receptors. α2 blockage increases the sympathetic flow-> increase in HR and FC. Hence they are not preferred except in pheochromocytoma.

Specific α1 blockers- Prazosin, terazosin, doxazosin. They are selective α1 blockers. α1 stimulation produces vasoconstriction. Blockage of these receptors result in vasodilatation-> decrease in PR-> fall in BP. Vasodilatation occurs in both arteries and veins. Arterial dilatation causes decrease in PR, this decrease diastolic BP. Venodilatation decreases the venous return and cause decrease in CO and decrease in systolic BP. They also decrease TG, LDL and increase HDL.

5. β blockers- Non selective **β blockers**- Propranolol, **β1 blockers-** atenolol, metaprolol,

MOA: .β1 receptors are located in the heart (pace maker cells and myocardial cells).

β1 receptors belongs to Gs type of G protein coupled receptors. Adrenaline/NA are the agonist for these receptors. Propranalol, atenolol or metaprolol are the antagonists for these receptors as they have only affinity with these receptors. The blockage of β1 receptors in the pacemaker cells by these drugs causes decrease in HR. The blockage in the myocardial cells decreases the force of heart contraction. This decreases the cardiac output. The decreased CO leads to decreased systolic BP. Initially peripheral resistance (PR) increased, then normal and later there is marked decrease in the PR. This decreases the diastolic BP also. The beta blockers also block the β1 receptors located in the juxta-glomerular cells of the nephrons. The blockage by beta blockers decreases renin secretion and rennin decreases the BP through rennin-angiotension-aldosterone pathway.

6. Calcium channel blockers (CCB) - Verapamil, diltiazem, nifedipine, amlodipine.

Mechanisms-

1.In cardiac cells troponin-tropomycin system prevents the interaction between actin and myosin. The calcium binding site present in the troponin. When adrenaline/NA binds to β2 (Gs) receptors, adenylyl cyclise (AC) gets activated. Activated AC stimulates the synthesis of cAMP (second messenger). The cAMP causes activation of cellular protein- protein kinase A. The activated PKC causes the phosphorylation of other proteins like calcium channels. This increases the calcium concentration within the cell. These calcium ions bind to binding sites present in the troponin molecules. This disturbs the tropomycin-toponin system. This leads to the interaction between actin-myosin, and causes muscle contraction. In presence calcium channel blockers these calcium channels get blocked. This causes muscle relaxation. This reduces the heart contraction and cardiac output. This decreases systolic pressure (sBP).

2. In vascular smooth muscle cells- When sympathetic nerves get stimulated vasoconstriction takes place. The released adrenaline/NA binds to α1 receptors (Gq type) and stimulates the PLC. This leads to the formation of IP3 and DAG. These second messengers lead to increased intracellular concentration of calcium. Calcium combines with calmodulin to form Ca2+ - CaM complex, which activates MLCK. Activated MLCK phosphorylates myosin LC-> myosin LC-(P). This leads to vascular smooth muscle contraction (vasoconstriction). When calcium channels are blocked, there is; decreased entry of Ca2+ into the cell, decreased release of Ca2+ from SR, reduction in intracellular Ca2+. Hence vasodilatation takes place. This decreases peripheral resistance (PR) and decreases diastolic BP. Thus calcium channel blockers reduce both systolic and diastolic B.P.

7.Angiotensin converting enzyme inhibitors- (ACE inhibitors)- Captopril, lisinopril, enalapril, ramipril, benazepril.

ACE inhibitors are the enzyme which inhibits the formation of angiotensin II. ACE is a membrane bound, zinc dependent dipeptidase that catalyzes the conversion of the decapeptide angiotensin I to the potent vasopressor octa-peptide angiotensin II by removing the two C-terminal amino acids. ACE is well known enzyme that regulates the BP through rennin-angiotensin-aldosterone pathway. Angiotensin II increases the BP by three ways-

a. Stimulates adrenal cortex. This increases the release of aldosterone. In the kidney aldosterone increases the tubular re-absorption of sodium and water. This increases blood volume and BP.

b.Angiotensin II also stimulates posterior pituitary gland. This increases the release of antidiuretic hormone (ADH). This hormone also increases the increases the tubular re-absorption of sodium and water. This increases blood volume and BP.

c. Angiotensin II directing act on the Angiotensin II receptors located on the vascular smooth muscles. This leads to vasoconstriction and increase in BP.

ACE inhibitors act by inhibiting the ACE. This decreases the formation of angiotensin II and BP.

8. Angiotensin receptor antagonist- Saralasin, losartan, telmisertan, valasertan, candesertan.

The angiotensin receptors (A1) are found in the heart, blood vessels, kidney, adrenal cortex, lung and brain. Its ligand is angiotension II. A1 receptors belong to G protein coupled receptors (Gq). When Angiotensin II binds to AI receptors the PLC get activated and the IP3 and DAG (second messengers) increase the calcium concentration within the cell. The calcium binds to Cal-calmodulin complex. This complex stimulates the MLCK and causes phosphorylation of MLC to MLC-P. This causes vasoconstriction and increase of BP. Angiotensin receptor antagonists act by blocking the A1 receptors. This causes vasodilatation and decrease of BP.

9.Direct acting vasodilators- Hydralazine, minoxidil, Na nitropresside-
Hydralazine is a direct acting smooth muscle relaxant used to treat hypertension by acting as a vasodilator primarily in arteries and arterioles. This decreases the peripheral resistance and BP. The exact mechanism of hydralazide is unknown. But it uses NO released from endothelium of the blood vessels for initiating its vasodilatory effect.
Minoxidil- Minoxidil is an antihypertensive vasodilator medication. It also slows or stops hair loss. At present it is available OTC for the treatment of alopecia. Minoxidil is a prodrug activated by sulfation (addition of sulphate group) via the sulfotransferase. Minoxidil is a potassium channel opener, causing hyperpolarization of cell membranes and causes vasodilation.
Na nitropresside is an inorganic compound. In the blood circulation Na nitropresside breaks to form NO. The NO diffuses into smooth muscle cell of blood vessel. NO activates guanylate cyclise and increases the concentration of cGMP. The cGMP activates protein kinase G. The activated protein kinase activates phosphatases, which inactivates myosin light chains by de-phophorylation (MLC-P - MLC). This causes vasodilatation and reduces the BP.

10.Aldosterone antagonist- **eg-Spiranolactone** Spiranolactone is a specific antagonist of aldosterone, actng primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted tubule. Spiranolactone causes increased amounts of sodium and water to be excreted, while potassium is retained. It acts both as a diuretic and as an antihypertensive drug.

11.Diuretics- Thiazides and loop diuretics- frusemide
Thiazides- Thiazide is a type of diuretic used to treat hypertension and edema (caused by heart, liver or kidney disease). The thiazides are the cheapest antihypertensive drugs. Thiazide act by inhibiting the Na+Cl- in the DCT. The sodium chloride symporters (co-transporters) are expressed on the cells of DCT. This increases the re-absorption of sodium and chloride ions into the blood vessels. Thiazide act by blocking these symporters. This decreases the re-absorption of sodium ions and BP. Loop diuretics (eg Frusemide) act by blocking the Na,2Cl,K symporters present on the cells of thick loop of Henley. This decreases the re-absorption of sodium and chloride ions.

b. Pharmacology of centrally acting drugs (Clonidine and methyldopa).
Clonidine HCl (catapress) - It is an imidazoline derivative. It is centrally acting α2 receptors agonist hypotensive agent.
Mechanism- It acts on α2 receptors (auto-receptors) located in the vasomotor center of the brain. The presynaptic membranes of the adrenergic nerve endings of the vasomotor center have α2 receptors. Upon stimulation the released adrenaline/Nor-adrenaline also binds to these receptors. These receptors belong to the Gi type of G protein coupled receptors. The activation of α2 receptors causes activation of K+ channel, closure of Ca2+ channel. This leads to hyper-polarization (IPSP). This decreases the secretion of nor-adrenaline and resulting in vasodilatation (due to decreased interaction between nor-adrenaline with alpha receptors located on the vascular smooth muscles). This decreases peripheral resistance in the blood vessels and diastolic BP. The decreased sympathetic activity also decreases force of contraction of the heart and cardiac output. This decreases systolic B.P. Thus clonidine decreases both diastolic and systolic pressure.
Metabolism- Clonidine is metabolized in the liver via minor pathway by different cytochrome 450 enzymes.. Four metabolites are formed. But one metabolite is identified that is 4 hydroxy clonidine. The metabolite and free drug (clonidine) are eliminated through urine. **ADRs**-

1.Drowsiness, sedation, constipation, dryness of mouth, nose, and eyes. 2. Impotence, salt and water retention, bradycardia 3. Postural hypotension (drop in BP due to change in body position). Fluid retention and edema is also a problem with chronic therapy, therefore, concurrent therapy with a diuretic is necessary. Sudden discontinuation of clonidine can lead to rebound hypertension, which is due to excessive sympathetic activity.

Uses- 1. It is used to treat moderate and severe hypertension. 2.For the diagnosis and treatment of Pheochromocytoma-. 3. Used for the treatment of diarrhoea in diabetic patients. 4. Prophylaxis of migraine. 5. Used in attention deficit hyperactivity disorder (ADHD).

Contraindications-- In pregnancy, lactating women.

Drug interactions- If clonidine is given along with alcohol may cause sedation, poor judgement, slowdown of reflexes.

Preparations- Clonidine HCl tablets, injection, transdermal patches.

α methyl-dopa (aldomet) –It is a centrally acting antihypertensive drug.

Mechanism- It is an antihypertensive drug and is the L-isomer of alpha-methyldopa. Its brand name is aldomet. It has a dual mechanism of action 1. It acts by inhibiting the enzyme DOPA decarboxylase (it converts L-DOPA to dopamine). This results in decreased formation of nor-adrenaline/adrenaline. This decreases B.P

2. Dopamine β-hydroxylase converts α methyl-dopa to methyl nor-adrenaline in the synaptic vesicles of the sympathetic nerves. The released methyl nor-adrenaline acts as false neurotransmitters for the alpha receptors present on the blood vessels. This interaction results in vasodilatation and decreases the BP.

Pharmacokinetics- Methyldopa exhibits variable absorption from the gastrointestinal tract. It is metabolized in the liver and the intestine and is excreted in urine. The important metabolites are methyl alpha methyldopa, methyl alpha dopamine, alpha methyldopa sulphate, alpha methyl dopamine.

ADRs- Sedation, lethargy, cognitive and memory impairment. Dryness of mouth, nasal stiffness, headache, fluid retention, weight gain, sexual dysfunction (libido, impotence), postural hypotension.

Uses- It is used in moderate to severe hypertension in combination with a diuretic. It is safe during pregnancy. It is not indicated in pheochromocytoma. It is indicated in gestational hypertension (pregnancy induced hypertension) and in pre-eclampsia (it is a disorder in pregnancy characterized by high blood pressure and a large amount of protein in the urine. Usually it occurs at third trimester of pregnancy).

Marketed Prep- Methyl dopa-125,250,500 mg tabs, 30mg/ml inj.

c. Classification of vasodilators including calcium channel blockers, Pharmacology of drugs affecting Renin Angiotensin system.

Classification of vasodilators used in hypertension

1. Calcium channel blockers (CCB) - Verapamil, diltiazem, nifedipine, amlodipine.

2.ACE- inhibitors- Captopril, lisinopril, enalapril, ramipril, benazepril

3.Angiotensin receptor antagonist- Saralasin, losartan, telmisertan, valasertan, candesertan.

4.Direct acting vasodilators- Hydralazine, minoxidil, Na nitropresside-

Pharmacology of drugs affecting Renin Angiotensin system.

Pharmacology of ACE- inhibitors- Captopril, lisinopril, enalapril, ramipril, benazepril

Captopril (trade name capoten) - It is an oral drug belongs to ACE inhibitors.

Mechanism- ACE inhibitors are the enzyme which inhibits the formation of angiotensin II. ACE is a membrane bound, zinc dependent dipeptidase that catalyzes the conversion of the decapeptide angiotensin I to the potent vasopressor octa-peptide angiotensin II by removing the

two C-terminal amino acids. ACE is well known enzyme that regulates the BP through rennin-angiotensin-aldosterone pathway. Angiotensin II increases the BP by three ways-

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c. Angiotensin II directing act on the Angiotensin II receptors located on the vascular smooth muscles. This leads to vasoconstriction and increase in BP.

ACE inhibitors act by inhibiting the ACE. This decreases the formation of angiotensin II and BP.

Pharmacokinetics- (ADME) - It is given by oral route before meals and its absorption is about 60 to 75%. If it is given after food its absorption decreases by 25 to 40%. After absorption in the blood about 25 to 30% bound to plasma proteins mainly albumin. The metabolism of captopril is mainly takes place in the liver. The metabolites- captopril-cystein disulfide and disulfide dimer of captopril are eliminated through urine.

ADRs- Skin rash, dry cough (due to the accumulation of bradykinins), hypotension, taste alterations, constipation or diarrhoea,

It is not recommended in pregnancy and lactating mothers as the drug passes through placental barrier and breast milk.

Therapeutic uses- ACE inhibitors are used for treating high blood pressure and heart failure. These drugs are also used for preventing kidney failure due to high BP and diabetes mellitus.

Marketed preparations-1.Captopril 25mg tab 2.Lisinopril 20mg tab, 3.Enalapril 20mg tab, 4.Ramipril 10 mg tab. 5.benagepril 10mg tab.

Pharmacology of Angiotensin receptor antagonists - Saralasin, losartan, telmisertan, valasertan, candesertan.

ARBs are drugs that block the action of angiotensin II by preventing angiotensin II from binding to angiotensin II receptors on the muscles surrounding blood vessels. As a result, blood vessels enlarge (dilate) and blood pressure is reduced. ARBs do not have adverse effect of dry cough.

Losartan-

Mechanism- The angiotensin receptors (A1) are found in the heart, blood vessels, kidney, adrenal cortex, lung and brain. Its ligand is angiotension II. A1 receptors belong to G protein coupled receptors (Gq). When Angiotensin II binds to AI receptors the PLC get activated and the IP3 and DAG (second messengers) increase the calcium concentration within the cell. The calcium binds to Cal-calmodulin complex. This complex stimulates the MLCK and causes phosphorylation of MLC to MLC-P. This causes vasoconstriction and increase of BP. Angiotensin receptor antagonists act by blocking the A1 receptors. This causes vasodilatation and decrease of BP.

Pharmacokinetics (ADME)- Losartan is well absorbed and undergoes first-pass metabolism. The systemic bioavailability of losartan is about 33%. In the blood it is bound to plasma proteins mainly to albumin. Losartan is metabolized by Cytochrome P-450 enzymes of the liver. It is metabolized to carboxylic derivative. The free drug and metabolites are eliminated through urine.

ADRs - Hypotension and tachycardia. Due to vagal (parasympathetic nerve) stimulation it causes bradycardia. No dry cough as there is no accumulation of bradykinin.

T. Uses- Used to treat hypertension. It is used to prevent stroke in patients with heart disease.

It is also used to prevent kidney disease in hypertensive patients with diabetes mellitus.

Marketed preparations- Losartan 100mg tabs, telmisetron 40mg tab, candesertan 8mg tab.

d.Angina pectoris and anti-anginal drugs classification-

These are the drugs used in the treatment of angina pectoris.

Angina pectoris: Angina pectoris, commonly known as 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.

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

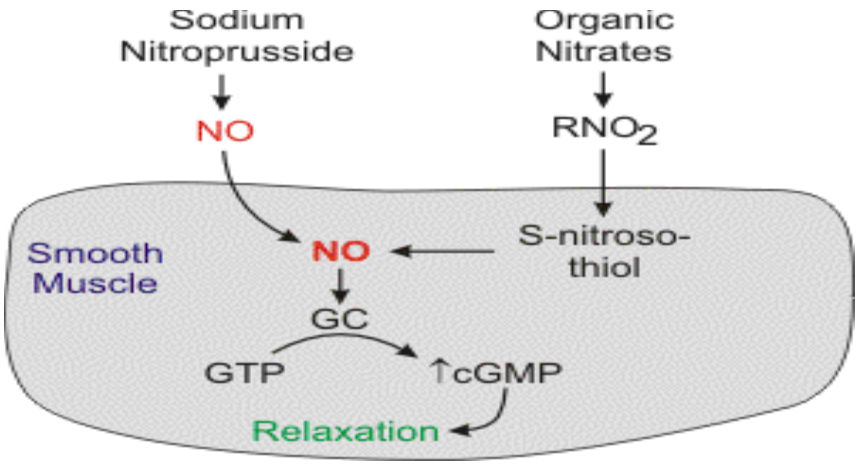
Drugs used in angina pectoris:

1.Organic nitrates: Amyl nitrite, isosorbide dinitrate, isosorbide trinitrate (nitro glycerine), isosorbide mononitrate, erythrytol tetranitrate, pentaerythrytol tetranitrate.
2. Beta blockers (propranolol, atenolol, metoprolol), CCBs (verapamil, nifedipine, deltiazem), K+ channel openers(nicorandil).
3.Antiplatelet drugs: Dipyridamole, aspirin, pentoxyphyllin.

Pharmacology of anti -anginal drugs.

1. Organic nitrates: Amyl nitrite, isosorbide dinitrate, isosorbide trinitrate (nitro glycerine), isosorbide mononitrate, erythrytol tetranitrate, pentaerythrytol tetranitrate.
2. Beta blockers (propranolol, atenolol, metoprolol), CCBs (verapamil, nifedipine, deltiazem), K+ channel openers(nicorandil).
3. Antiplatelet drugs: Dipyridamole, aspirin, pentoxyphyllin.

1.Organic nitrates: MOA: Within the body, organic nitrates are chemically reduced to release NO. No is an endogenous signalling 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 RNO2. The nitro group is reduced to form NO in the presence of specific enzymes and extracellular and intracellular reductants (e.g. thiols). The NO diffuses into the vascular smooth muscles. In the vascular smooth muscle cells the NO activates guanylyl cyclise (GC). The activated guanylyl cyclase increases the formation of cGMP (second messenger) from GTP. The cGMP activates myosin-LC phosphatase. The activated myosin-LC phosphatase causes the dephosphorylation of myosin-LC-(P) to myosin-LC. This relaxes the smooth muscle of coronary blood vessels and causes coronary vasodilatation.



Pharmacological actions of organic nitrates (nitro glycerine)

1. Vasodilatation: Organic nitrates dilate both arteries and veins.

a. Venodilatation (dilatation of veins): This decreases venous return. This reduces preload and end diastolic volume and pressure (EDVP). This also decreases the cardiac output. This decreases the size of the ventricles, intraventricular pressure and reduction in ventricular wall tension. This decreases the oxygen demand.

b. Coronary circulation: The larger coronary arteries get dilated. Smaller coronaries in ischemic region are already dilated in response to ischemia (lactic acid, adenosine, PGI2). This increases the blood flow to ischemic areas.

c. Arterial dilatation: Dilatation of larger arteries lead to flushing, headache. Dilatation of small arteries-> decreases PR-> decreases the DBP-> postural hypotension, reflex tachycardia.

d. Net effect on circulation: Decrease in venous return, reduction in CO, decreased SBP and SBP. Postural hypotension, palpitation, reflex tachycardia, flushing, headache are the side effects of these actions.

2. Oxygen demand: It is decreased.

3. Other smooth muscles: Relaxation of smooth muscles of gall bladder, biliary, sphincter of oddi, bronchial, GIT, urinary tract.

4. Antiplatelet effect: Nitrates have some antiplatelet action also.

ADME: Nitro-glycerine (NTG) administered by sublingual route, oral, transdermal ointment, intravenous route. Amyl nitrite is given by inhalation route. Nitrates undergo rapid first pass metabolism.

Sub lingual route: Quick onset of action, liver is bypassed; action is terminated by spitting out the tablet. This route is preferred for treating acute attack of angina pectoris.

Oral route: Onset of action is about 90 min, duration-3-6h. This route is used for long-term prophylaxis.

IV- NTG- it is used in unstable angina, MI with LVF and in hypertensive emergencies.

Instructions to the patient: Nitrates should be taken in sitting or supine position to avoid postural hypotension. The tablet should be spitted or swallowed once the pain subsides or headache occurs.

ADRs: **1.Due to VD:** Headache, giddiness, postural hypotension, flushing, dizziness (cloudiness of conseousness).

2. **Tolerance:** Tolerance develops with continuous use.

3. Dependence: Sudden withdrawal can lead to vasospasm, MI and death.

sUses:1.Used in angina pectoris. 2.In MI. 3.In LVF. 4. In HT crisis. 5. In cyanide poisoning. 6. In biliary colic, oesophageal spasm.

Beta blockers: β blockers decrease HR, FC and oxygen demand. Beta blockers are good for stable angina. β blockers are not coronary dilators. They decrease the FC-> incomplete systolic ejection-> increase EDV/P (it is a disadvantage). Sudden withdrawal can precipitate MI. Cardio selective β blockers should be preferred. β blockers are contraindicated in variant angina. Non selective blockers block both β1 and β2 receptors. β1 receptors cause vasodilatation. Blockage of β2 receptors leaves α1 receptors un-opposed. α1 receptors cause vasoconstriction. Thus vasodilator mechanism is blocked. This can precipitates the variant (vasospastic) angina. Beta blockers are useful in unstable angina and non ST- Elevation MI.

Calcium channel blockers:

a. **In stable (exertional) angina;** CCBs decreases the HR, FC -> decreases the oxygen demand by the heart (verapamil, diltiazem). They cause arterial dilatation -> PR decreases-> reduction in oxygen demand. VD causes reflex tachycardia (ADRs). They also cause coronary dilatation, increased blood supply. Dilatation occurs in large and small coronaries, blood goes to ischemic as well as non ischemic areas.

b. **In variant (vasospastic) angina:** Nifedipine is useful because of vasodilator action.

c. **In unstable angina:** Nifedipine + β blocker + aspirin. CCBs are not first choice drugs.

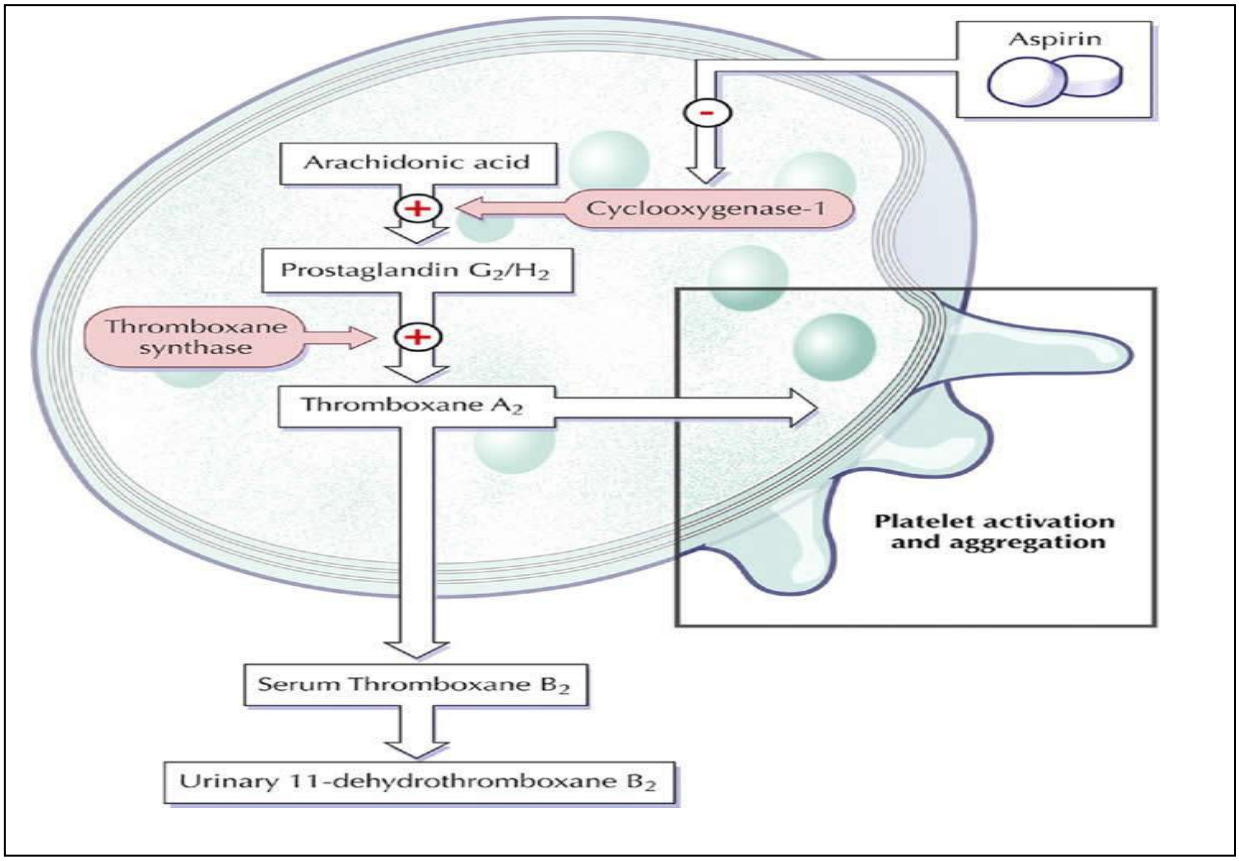
2. Miscellaneous drugs:

a. K+ Channel openers: e.g. Nicorandil. They are coronary dilators. They dilate small as well as large coronaries. Action is due to hyperpolarization of vascular smooth muscles leading to relaxation and also through nitrate like actions.

ADRs: Headache, palpitation, dizziness, nausea and vomiting.

CI: LVF, hypotension.

b. **Antiplatelet drugs**: e.g. Aspirin. The antiplatelet drugs decreases platelet aggregation and decreases thrombus formation. This prevents the development of atherosclerotic plagues in the blood vessels. Aspirin inhibit the cycloxygenase (Cox I and II) enzymes, this decreases the formation of thromboxane A2 from arachidonic acid.



Aspirin act by inhibiting the synthesis of thromboxane A2. Normally thromboxane A2 causes platelet aggregation by binding to the thromboxane A2 receptors expressed on the platelets. Low doses of aspirin may be given after a heart attack (MI) to reduce the risk of another attack. Aspirin is used in stable and unstable angina pectoris. Aspirin is also used in long term, at lower doses, to prevent heart attacks, strokes, and blood clot formation.

Anti-arrhythmic drugs; Classification and mechanism of action, Pharmacology of quinidine (A proto type sodium channel blocker).

d.Antiarrythmic drugs

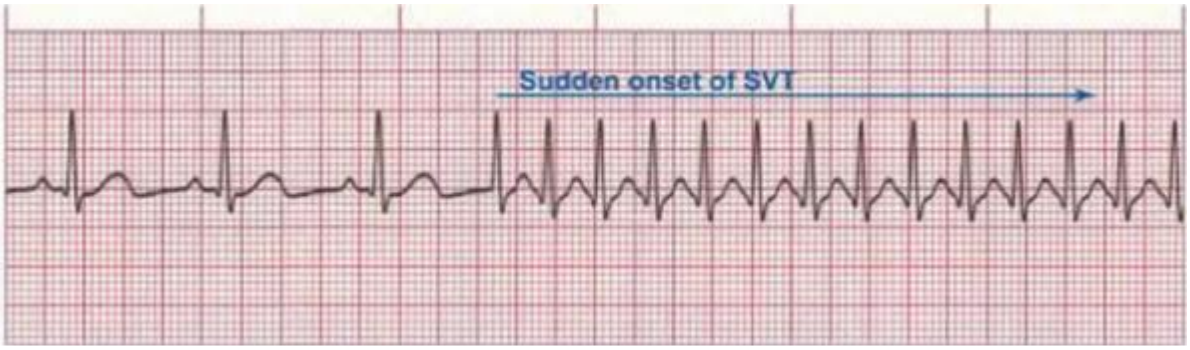
Arrhythmia means disturbance of rate, regularity, origin or conduction of cardiac impulse.

Cardiac arrhythmia is a group of condition in which the heart rate is irregular, too fast or too slow. If the beat is more than 100beats/min then it is tachycardia, and if below 60 beats/min then it is bradycardia. There are four main types of arrhythmias- extra beats, supra-ventricular tachycardia, ventricular arrhythmia and brady-arrythmia.

a. Extra beats- There are two types- premature atrial contractions and premature ventricular contractions.

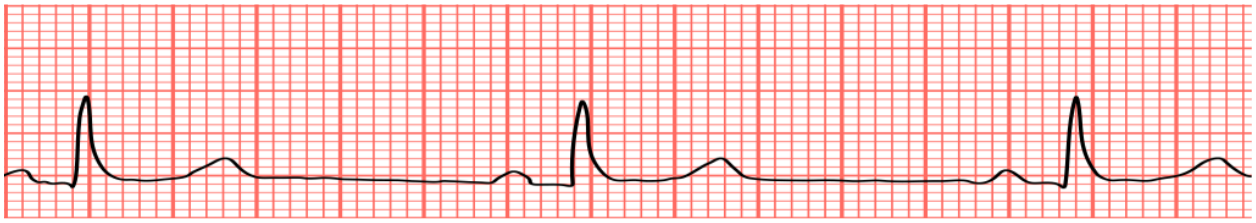
b. Supra ventricular tachycardia- It is due to improper electrical activity and is arises from sinuatrial node (SAN). The heart rate may increases to 200 beats / min.

Supraventricular tachycardias include atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia (PSVT).

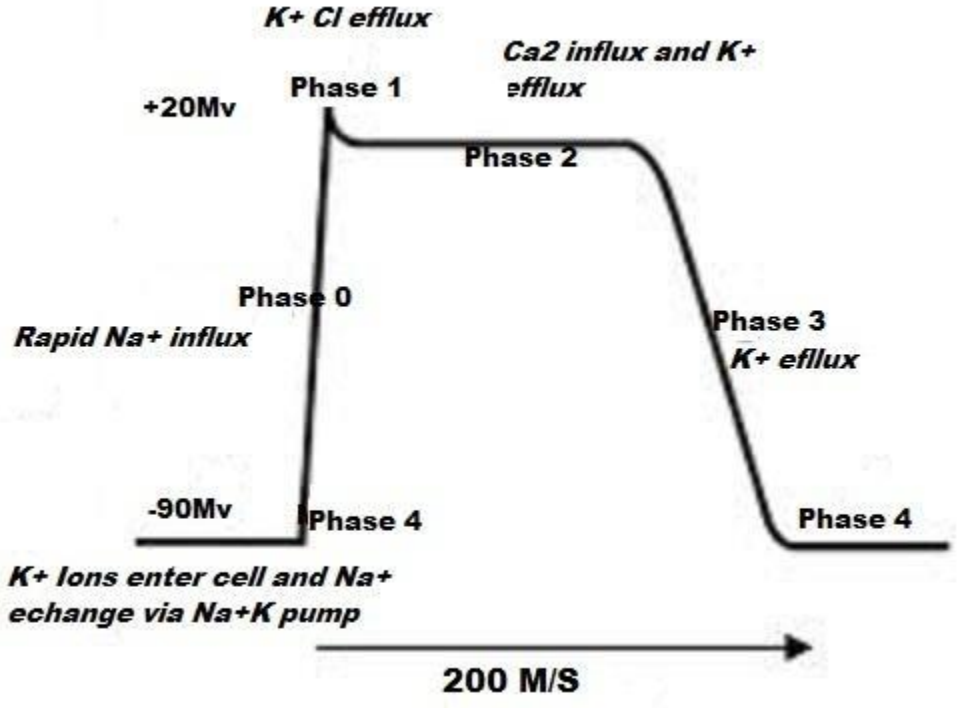


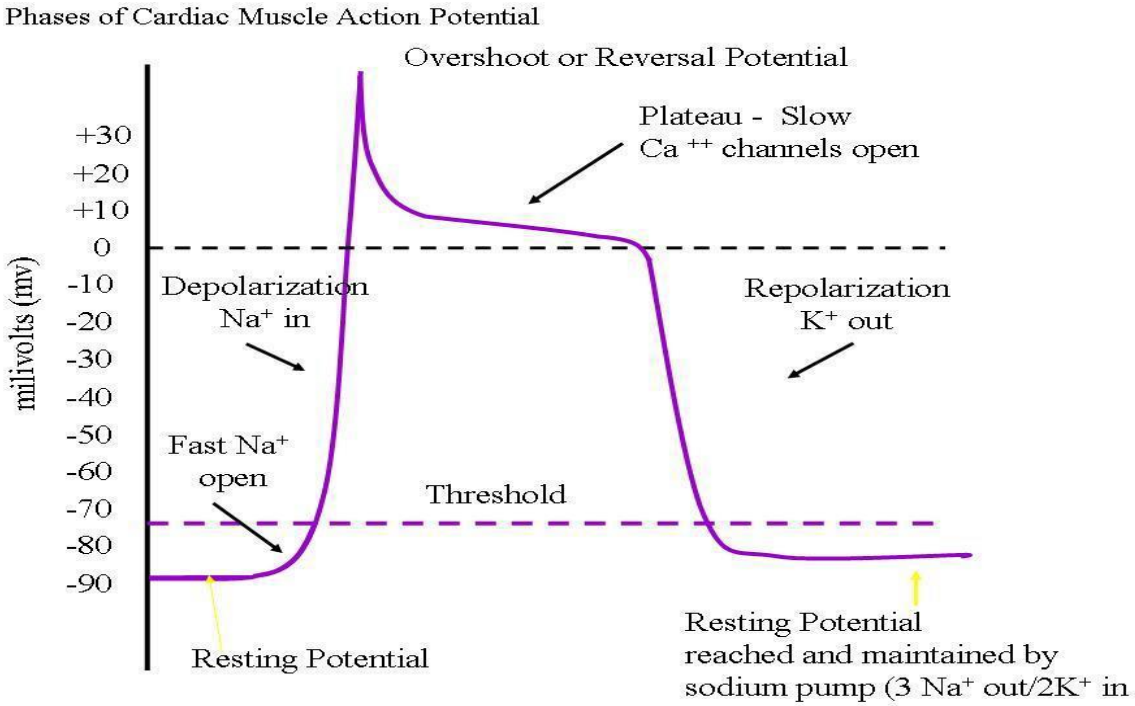
c.Ventricular arrhythmias- These include ventricular fibrillation and ventricular tachycardia.

d.Bradarrythmias- It is a type of arrhythmia in which the heart decreases below 60beats/min.



Electrical activity of heart

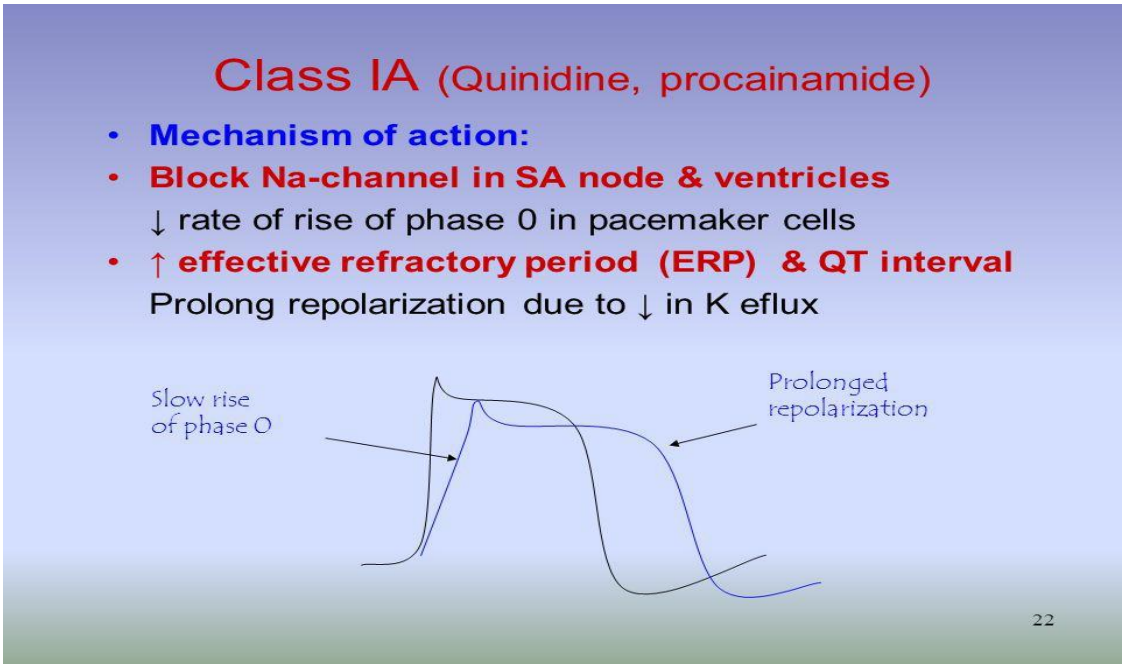




Phase O: **Rapid depolarization**, resting potential is -90 mV. Opening of Na+ channel, Na+ gets accumulated, potential increases to +20mV.

Phase-1: **Partial repolarization,** due to stoppage of Na+ channel + transient outward K+. Voltage becomes 10 mV.
Phase-2: Plateau phase. Voltage remains + ve (inside) -> voltage gated Ca2+channels get open – influx of Ca2+ from ECF and sarcoplasmic reticulum. Closure of Ca2+ channels at the end.
Phase -3: Rapid repolarisation: is due to outward of K+ plus stoppage of Ca2+influx. Resetting of resting potential to -90mV.
Phase-4: Diastolic depolarization: It is due to slow inward of Na+ current.
Electrical activity is disturbed in cardiac arrhythmias.

Classification of antiarrythmic drugs: There are 5 classes of antiarrythmic drugs:
Class I. Membrane stabilizing agents. (Na+ channel blockage).
a.Quinidine, procainamide,disopyramide, **b**.lidnocaine, tocainide**, c.**flecainide, encainide
Class II. β blockers: Propranolol, esmolol, sotalol
Class III. K+ channel blockers: Amiodarone, bretylium
Class IV. CCBs: Verapamil, diltiazem
Class V. Others: Digitalis, atropine, isoprenaline, adenosine.
Mechanisms of antiarrythmic drugs
Class I. Membrane stabilizing agents. (Na+ channel blockage).
a.Quinidine, procainamide,disopyramide, **b**.lidnocaine, tocainide**, c.**flecainide, encainide



It is a stereoisomer of quinine an alkaloid obtained from cinchona bark. It decreases the excitability of the cardiac muscle by blocking the sodium channels across the pace maker cells of the SAN and cardiac muscles. This decreases the rise of phase o in pacemaker cells. This also increases effective refractory period (ERP) and QT interval and prolongation of QRS, PR, and RR intervals. This also leads to prolonged repolarisation due to decreased K+ efflux. Thus heart rate decreases.
Class II. β blockers: Propranolol, esmolol, sotalol
MOA: They have two types of actions. Membrane stabilizing action (because of the blockage of Na+ channel, reduces inflow of Ca2+ ions during phase-0) and beta blocking action. They block the beta1 receptors present on the SAN and AVN. This decreases HR and force of heart

contraction. Due to blockage of β1 receptors, all the effects are antagonized. Thus HR, conduction velocity (CV) and automaticity (ability of the cardiac cells to depolarize spontaneously) is reduced, which in turn decreases the contractility of the myocardium.

Class III. K+ channel blockers: Amiodarone, bretylium,sotalol

Amiodarone: They act by blocking K+ channel. Because of this blockage the efflux of K+ ions from myocardial cells to interstitial fluid is restricted. This decreases the repolarisation. This increases the duration of each beat. In the ECG it increases the QT, PR and RR interval. Also block Na+, Ca2+ channel and blocks beta receptors. They decrease the conduction velocity.

Class IV. CCBs: Verapamil, diltiazem

Antiarrythmic action is due to voltage sensitive Ca2+ channels blockage. This decreases the conduction velocity of the cardiac impulse and decreases the heart rate. CCBs also cause VD of arteries and veins. There is reduction in PR and CO. They decreases both SBP and DBP,

Class V. Others: Digitalis, atropine, isoprenaline, adenosine.

Pharmacology of quinidine

Class I a. Quinidine- It is a stereoisomer of quinine an alkaloid obtained from cinchona bark. It decreases the excitability of the cardiac muscle by blocking the sodium channels across the pace maker cells of the SAN and cardiac muscles. This decreases the rise of phase o in pacemaker cells. This also increases effective refractory period (ERP) and QT interval and prolongation of QRS, PR, and RR intervals. This also leads to prolonged repolarisation due to decreased K+ efflux. Thus heart rate decreases.

Other actions of quinidine- It has anti-malarial action, inhibition of skeletal muscle contractility. At higher doses it increases the contractions of uterus and GIT.

ADME- Quinidine is almost completely absorbed from the GIT. However, because of hepatic first-pass effect, the bioavailability is about 70- 80%. But no difference observed between the rate of quinidine absorption, when given by intramuscular injection or oral absorption. About 70 to 80 % of the drug bound to plasma protein. Plasma protein is decreased in patients with chronic liver disease. Quinidine concentrations in liver are 10 to 30 times higher than those in plasma. 50 to 90% of quinidine is metabolized in the liver to hydroxylated products -eg.4-hydroxyquinidine. The principal metabolite is 3 hydroxyquinidine which exerts similar effects to quinidine. The metabolites and free drug eliminated through urine.

Preparations- Quinidine gluconate 324mg controlled release (CR) tabs, quinidine sulfate 200mg, 300mg tabs.

ADRs-

1. Idiosyncratic reactions- fever, angioedema (swelling under the skin due to the vascular leakage), asthma, thrombocytopenia, hepatitis.
2. GIT- Nausea, vomiting and diarrhoea.
3. CVS- precipitates CCF
4.Cinchonism- ringing in ears, deafness, vertigo, headache, and visual disturbances.

Drug interactions:

1. If it is given with digitalis, the quinidine displaced from its binding sites and increases the toxicity.
2. With vasodilators-> more vasodilation.
3. With diuretics-> hypokalemia.
4. With beta blockers/CCBs-> myocardial depression.

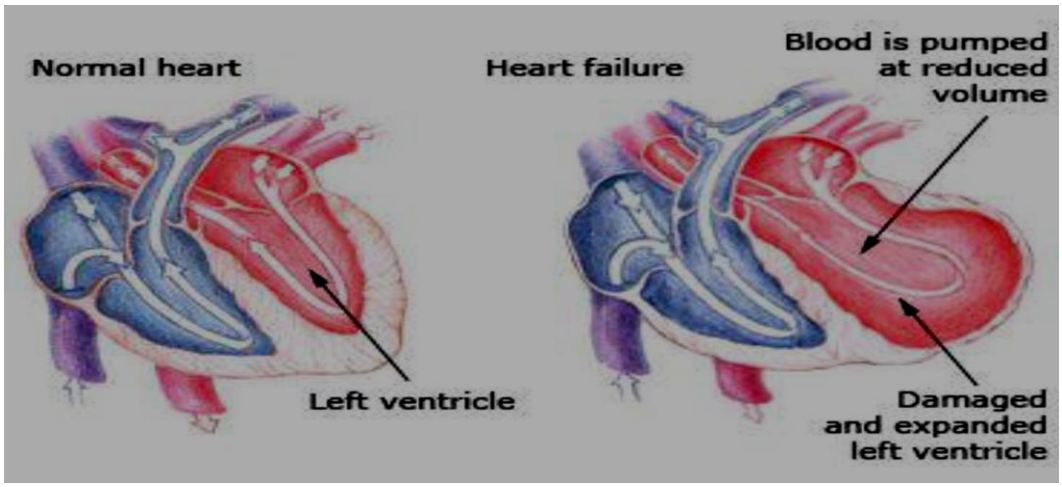
s**Uses** – Used in supra-ventricular tachycardias- Atrial flutter, atrial fibrillation, PSVT.Drugs used for therapy of congestive cardiac failure (CCF); Classification and mechanism of action of drugs used for CCF, Pharmacology of digoxin.

c) Drugs used for therapy of Congestive Heart Failure

Congestive Heart Failure: It is a chronic progressive condition that affects the pumping power of the heart muscles. Heart failure may be LVF, RVF or both.

a. Left ventricular failure (LVF): when left ventricle fails to pump adequately, there is incomplete ejection of blood from the left ventricle. This results in decrease in cardiac output (CO). (Stroke volume x HR= CO 70x72= 5Lt). The decreased CO leads to the less blood supply to the body tissue. This causes fatigue and decreased tolerance to the exercise. The oxygenated blood remains in the left ventricle. This increase end systolic volume (more than 60ml). Ventricular filling continues and this leads to the dilatation of the ventricles. The length of the myocardial muscle fibers increases. This slowly develops into hypertrophy of myocardium (remodelling of heart) or enlargement of the ventricle. The dilated left ventricle fails to increase force of contraction. The accumulated blood within left ventricle leads to the development of back pressure. The blood goes back to the left atrium. The left atrial pressure increases. The oxygenated blood goes back to the lungs. This causes pulmonary congestion and pulmonary oedema. The fluid gets accumulated in the alveoli. This impairs the gas exchange and oxygenation of blood. This leads to hypoxia and breathlessness.

The decreased supply of blood stimulates the sympathetic nerves. This increases HR, vasoconstriction and force of contraction (but this is not possible). The decreased CO decreases renal blood flow. This decreases urine output. This causes Na and water retention. This increases blood volume, increased load on the heart. This also stimulates the rennin-angiotension activity. The decreased CO also reduces cerebral blood flow. This causes confusion and coma.



Right ventricular failure (RVF) - RVF occurs as a result of LVF. In RVF the deoxygenated goes back to the right atrium and into the superior and inferior venacava. The blood also goes to the liver through hepatic vein. This leads to the congestion and enlargement of the liver (hepatomegally). The back flow also leads to peripheral oedema noticeable near the limbs. The RVF also leads to ascites (accumulation of the fluid in the abdomen leading to hanging abdomen)..

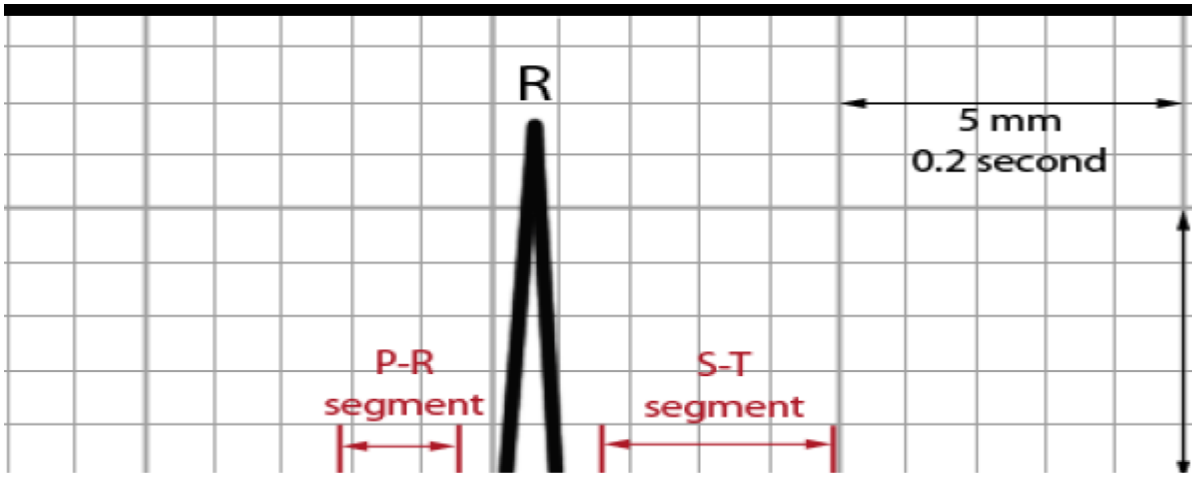
Drugs used in CCF:

1.Cardiotonic drugs: Cardiac glycosides- Cardiac glycosides are present in the digitalis plant.
Eg. Digoxin, digitoxin,gitoxin, lanatoside, quabain.

2.Vasodilators- a. ACE-I: e.g. Captopril, enalapril and lisinopril.
b.ARBs (Angiotensin receptor antagonist) e.g Losartan.
c.Nitrovasodilators (organic nitrates)- e.g. Glyceryltrinitrate (isosorbide trinitrate), isosorbide dinitrate.
d.Direct vasodilators: e.g.Sodium nitroprusside, Hydralazine and nicorandil.
e.CCBs: e.g.Nifedipine, and amlodipine.
f. Phosphodiesterase III inhibitors: e.g.Amrinone, milrinone.
3.Adrenergic receptor antagonists- Prazosin (α1 blocker), phentolamine (α1and α2 blocker).
4. **β1 receptor agonists**- Dobutamine.
5. **Diuretics**- e.g. Hydrochlorthiazide, frusemide and amiloride.
Pharmacology of digoxin- Digoxin is the purified cardiac glycoside extracted from the plant digitalis lanata.
1.Cardiotonic drugs: Cardiac glycosides- Cardiac glycosides are present in the digitalis plant.
Eg. Digoxin,digitoxin,gitoxin, lanatoside,quabain.
Digitalis: Two sources of digitalis are *D.purpura, D.lanata*. The important glycosides present in digitalis are digitoxin, gitoxin, digoxin, lanatoside. They are steroidal glycosides containing steroid nucleus. Each glycoside is made up of an aglycone (genin) and a sugar. The aglycon part is responsible for its pharmacological activity. The sugar part increases the pharmacokinetic properties like water solubility, cell permeability and potency of the aglycone.
Pharmacological actions of Digoxin:
1. **Heart**: a. **Force of Contraction**: It is increased. This is known as +ve ionotropic effect. Contractions are more powerful. The duration for the systole decreases and for the diastole it is increases. There is more complete emptying. This increases cardiac output (CO) and reduces the size of the chambers.

(i) Better tissue perfusion. The increased CO results in decreased sympathetic tone. It reduces the heart rate, vasoconstriction.

(ii) Increase in renal flow- The increased CO also increases urine output. This decreases circulating volume, decrease in edema.
(iii) Better emptying of the left ventricle- This reduces the back pressure, pulmonary pressure. This decreases pulmonary edema. This improves breathlessness problem.
Increase in FC and CO by digitalis is without corresponding increase in oxygen demand.
b. Heart Rate (HR) is decreased due to increase in cardiac output (CO) and decrease in sympathetic tone. The decreased HR is also due to the stimulation of vagus (parasympathetic) nerve by the digitalis
c. Electrophysiological effects: Reduces SAN automaticity (vagal action + direct action at toxic doses). In AV node it decreases CV (conduction velocity). In the ventricles it increases automaticity. Increase in excitability. On ECG digitalis prolongs PR interval and depresses the ST segment.



2. Kidneys: Increase in urine output- secondary to increase in CO (digitalis does not have diuretic action or direct action on kidneys).
3. CNS: Higher doses activate chemoreceptor trigger zone (CTZ present in the medulla oblongata and is communicated with vomiting centre to initiate vomiting) and causes nausea, vomiting. Other CNS actions due to higher doses of digitalis are hallucinations, visual disturbances, disorientation, mental confusion, etc.

MOA: The cardiac glycosides (digoxin) act by inhibiting the Na+-K+ ATPase enzyme activity (pump). This enzyme present on the myocardial cells. This pump ensures the transmembrane stransfer of the cations Na+ and K+. This pump consists of two alpha catalytic subunits and of two beta subunits. This pump uses the energy released by the hydrolysis of the ATP in the presence of magnesium to ensure the transport of 3 Na+ ions to outside the cells and of 2 K+ ions to inside. The inhibited enzyme cannot exchange Na+ ions for K+ ions. Thus all Na+ ions remain inside the cell and its concentration is increased in the cardiac muscle. Increased concentration of Na+ increases the transportation of Ca2+ from extracellular fluid (ECF) into the cell across the cell membrane by Na+/Ca2+ exchange mechanism. One molecule of extracellular Ca2+ is exchanged for 3 molecules of intracellular Na+. Increased concentration of intracellular Ca2+ triggers the release of large amounts of Ca2+ from the internal stores of sarcoplasmic reticulum into cytoplasm. Thus more of Ca2+ is available inside the cell. The Ca2+ bind with the binding site present on the troponin, this disturbs the troponin-tropomycin system. This causes the interaction of actin-myosin contractile proteins and brings about myocardial contraction. Advantage of digitalis is that it increases force of contraction without increasing corresponding increase in the O2 demand.

ADME- About 70 to 80% of oral dose of digoxin is absorbed, mainly in the intestine. The degree of binding to serum albumin is 20 to 30%. Digoxin is extensively distributed in the tissues-heart, kidney and skeletal muscles. The main route of elimination is renal excretion. About 25 to 28% of digoxin is eliminated by non renal routes. Nearly all of the digoxin is eliminated unchanged, with a small part as active metabolites.

ADRs:
1. Anorexia, nausea, vomiting- due to gastric irritation + stimulation of CTZ.
2.CNS: Headache, malaise (uneasiness), fatigue, drowsiness, weakness, paresthesia (abnormal sensation), disorientation, confusion, delirium (acute confusional state), hallucinations, convulsions.
3. Cardiac adverse effects: sinus bradycardia (due to increase vagal tone), AV block (partial or complete).

Drug interactions:
1. With quinidine increases the blood levels of digoxin by decreasing tissue binding of digoxin.
2.With amphotericin B results in hypokalemia, this increases digoxin toxicity.
3.With calcium increase the toxicity of digoxin.
4.With antacid digoxin absorption decreases.
5.With pentobarbitone metabolism of digoxin increases and decreases its toxicity.
6. With srythromycin digoxin metabolism decreases and toxicity increases.
CI: Hypokalemia, hypercalcemia
Uses:
1. Congestive cardiac failure
2.Left ventricular failure
3.Paroxysmal supraventricular failure (PSVT)
4.Atrial flutter
5.Atrial fibrillation.
Preparations- Digoxin tabs, inj

Drugs used in treatment of hyperlipidaemias;
Hyperlipidemia- It is a disorder which occurs due to the elevated levels of lipids (cholesterol and triglycerides) in the blood. There are two types- hypercholesterolemia and hypertriglyceridemia.
Hypercholesterolemia- It is due to high cholesterol in the blood.
Hypertriglyceridemia. It is due to high triglycerides in the blood.
Hypercholesterolemia- Cholesterol is a sterol (steroid alcohol). Cholesterol is essential for the formation of cell membrane, vit D, steroid hormones and bile acids. Since cholesterol is insoluble in water, it is transported in the blood in the form of lipoproteins. Lipoproteins are classified on the basis of density into- VLDL, LDL, IDL and HDL. All lipoproteins carry cholesterol, but elevated levels of the lipoproteins other than HDL are associated with an increased risk of atherosclerosis and coronary heart disease. The higher levels of HDL cholesterol are protective.
Long term elevated levels of cholesterol results in atherosclerosis. This may lead to stenosis (narrowing) and occlusion of the arteries. A sudden occlusion of a coronary artery results in a myocardial infarction or heart attack. An occlusion of an artery supplying brain can cause a stroke. Hypercholesterolemia also leads to xanthelasma palpebrarum (yellowish patches near the eyelids, xanthomas (deposition of yellowish cholesterol rich material). Normal total cholesterol is 180-200mg/dL. xanthoma

Hypertriglyceridemia- Elevated levels of triglycerides also associated with atherosclerosis even in absence of hypercholesterolemia. Very high triglyceride levels also increase the risk of acute pancreatitis, xanthomas.

Drugs used in hyperlipidemias- Classification:

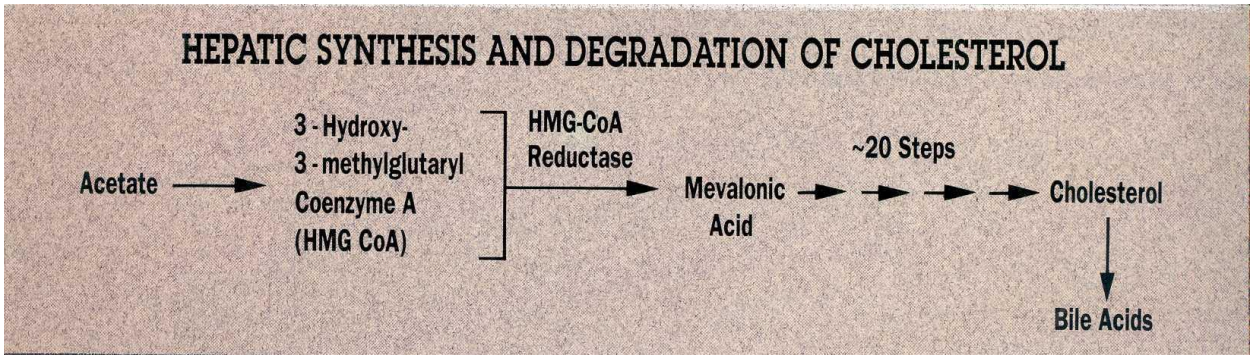
1. HMG-CoA Reductase Inhibitors (Statins) :Lovastatin, simvastatin, pravastatin, atorvastatin.
2. Bile acid sequestrants (resins): Cholestyramine, colestipol.
3. Lipoprotein lipase activators: Clofibrates, gemfibrozil, bezafibrate, finofibrate.
4. TG synthesis inhibitors: Nicotinic acid
5. Others: Probucol, gugulipid.

1.HMG-CoA Reductase Inhibitors (Statins): **Pharmacology of atorvastatin-**

Pharmacological actions and MOA: During the synthesis of cholesterol, the 3-hydroxy 3-methyl glutaryl Co-enzyme A (HMG CoA) reductase which converts HMG CoA to mevalonic acid. The mevalonic acid is then (after 20steps) converted into cholesterol. Statins act by inhibiting the HMG-CoA Reductase, thus cholesterol synthesis decreases. This leads to increase expression of LDL receptors in hepatocytes. This increases the uptake of IDL and LDL into the liver.

Cholesterol biosynthesis occurs mainly during sleep. Hence statins should be given at bed time. Atorvastatin is a long acting drug; this can be given at any time. Combination with cholestyramine or nicotinic acid enhances LDL lowering effect.

Statins also act by increasing the production of nitric oxide and this NO prevents the oxidation of LDL. Grape fruits interferes the metabolism of statins and hence the combination should be avoided.



ADME- Statins are administered orally. Most statins bind with plasma proteins. Most of administered statins undergo first pass effect. Only 5-20% of the drug reaches the systemic circulation. The statins are metabolized in the liver. The statin metabolites are excreted through the bile and urine.

ADRs:

1. Myopathy syndrome- Myalgia in the arms, legs and in the entire body.
2. Rhabdomyolysis- (Rapid breakdown of muscle tissue-release of myoglobin-> kidney toxicity due to its accumulation.)
3. Other common side effects: Dyspepsia (indigestion), flatulence (excessive gas in the GIT) and abdominal pain.

Therapeutic uses: Statins are used to reduce cholesterol level in hypercholesterolemic patients. Lipitor (atorvastatin) is the world top selling drug.

2. **Bile acid binding resins-**: Cholestyramine, colestipol.
Pharmacological actions and MOA: Both are water insoluble resins. They are unaffected by digestive enzymes and are not absorbed in GIT. In the liver cholesterol is converted into bile acid. The bile acids are excreted through bile. The bile acids help in absorption of cholesterol. These drugs bind with bile acids in the intestine and thus increase fecal excretion of the bile acids. This increases the excretion of fat through feces. Inhibition of the return of bile acids to the liver results in an increase in conversion of cholesterol to bile acids. This stimulates the cholesterol synthesis in the liver. This leads to the more expression of LDL receptors in the liver. This increases the uptake of LDL. Hence the plasma LDL level decreases.
ADRs: Nausea, vomiting, constipation, bad taste, steatorrhea (presence of excess fat in feces.), aggravation of haemorrhoids.
Preparations and dose: Cholestyramine-12-24g/day, colestipol 15-30g/day.
Uses - In hypercholesterolemia.

3. Lipoprotein lipase activators: Clofibrate, gemfibrozil, bezafibrate, finofibrate
MOA : Clofibrate increases the activity of extra-hepatic lipoprotein lipase (LL), thereby increasing the triglyceride lipolysis from chylomicrons. This decreases the blood triglyceride level.
ADME: All fibrates are administered orally. Its absorption is more if taken with meals. Its absorption decreases when taken on an empty stomach. About 95% of the drug bound to plasma proteins like albumin. Fibrates gets metabolized in the liver and the metabolites are excreted through the urine.
Therapeutic uses: It is the drug of choice for the treatment of hyperlipidemics with high TG levels. Clofibrate is now rarely used because it increases the lithogenicity of bile (gall stones).
Contraindications: In hepatic dysfunction and renal failure.
ADRs: Epigastric distress, loose motions, head ache, body ache, blurred vision.
Doses: Gemfibrozil 600mg- Caps, Bezafibrate-200, 400mg tab, Fenofibrate- 200 mg.caps Classification and mechanism of action of anti- hyperlipidaemics, Pharmacology of atorvastatin (A proto type of HMG CoA reductase inhibitor).