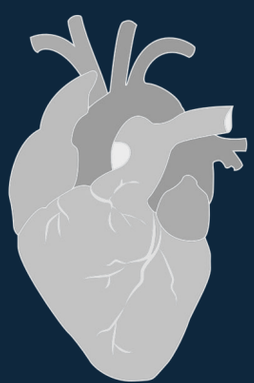
PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY



SUMMARY
CVS block

- Important
- In male and female slides
- Only in male slides
- Only in female slides
- Extra information

Helpful flash cards ♦

Editing file

Sympatholytic & adrenergic blockers α-receptor Antagonists

Drug	Classification	MOA	Uses	Adverse Effect	Contraindication
a-Methyl dopa	Adrenergic neuron blockers	**-** Formation of false transmitter **-** Stimulation of presynaptic α2 receptors.	- Treatment of **hypertension in pregnancy** (gestational hypertension & pre-eclampsia)	-	-
Guanethidine		**-** Inhibition of release and enhance uptake.	-	-	-
Clonidine		**-** Stimulation of presynaptic α2 receptors.	- Little used as antihypertensive agent.	**- rebound hypertension** upon abrupt withdrawal (so Little used as antihypertensive agent).	-
Apraclonidine			- is used in open angle **glaucoma** as eye drops. (acts by decreasing aqueous humor formation)	-	-
Reserpine		**-** Interferes with NA storage.	-	-	-
Phenoxybenzamine	Adrenergic receptor blockers	- **Irreversible** block of both α2 and α1 receptors (long-acting 24 hrs)	- Pheochromocytoma.(before surgical removal).	- Postural hypotension. - Tachycardia. - Headache. - Nasal stuffiness or congestion. - Vertigo & drowsiness. - Male sexual dysfunction (inhibits ejaculation).	- **patients with decreased coronary perfusion.** - can precipitate arrhythmias and angina.
Phentolamine		- **Reversible** blocking of α2 and α1 receptors (short acting 4hrs)			
Prazosin		-Selective α1-Antagonists (short half life)	- Urinary obstruction of benign prostatic hypertrophy (BPH). - Treatment of essential hypertension with prostate enlargement. - Reynaud's disease.	- Vasodilatation. - ↓ arterial pressure. - less reflex tachycardia. - First dose may produce an orthostatic hypotensive response can result in syncope (fainting).	-
Doxazosin		- Selective α1-Antagonists (long half life)			-
Terazosin					-
Tamsulosin		- **Selective α_{1A}-antagonists** (which present in prostate)	- benign prostatic hypertrophy (BPH).	as non selective but to a lesser degree	-
Yohimbine		- α2 -selective antagonists	- Used as aphrodisiac in the treatment of erectile dysfunction.	-	-

β- Adrenoceptors blockers

MOA	β- adrenergic blockers
Contraindications	- Heart Block. - Diabetic patients. - Hypotension. - Bronchial Asthma and emphysema (safer with β1-selective blockers). - Peripheral vascular disease like Reynaud's disease (safer with β1-selective blockers). - Alone in pheochromocytoma (must be given with an α-blockers).
Pharmacological actions	-CVS: Negative inotropic, chronotropic, dromotropic, ↓CO. - Antianginal effects. - mask hypoglycemia in diabetic patients> coma. - blood vessel β2: ↑peripheral resistance, ↓Blood flow to organ. - Hypoglycemia, ↓lipolysis in adipocytes B3,Na^+ retention 2^{ndry} to ↓BP. - Antiarrhythmic effects. - Antihypertensive. - Bronchoconstriction. - Intestinal motility. - Reduce intraocular pressure.
Adverse Effects	Unwanted pharmacological actions.

Drug	Pharmacodynamic Classification	Pharmacokinetic Classification	Uses	Adverse effects
Propranolol	- Non-selective block β1& β2. - Without intrinsic sympathomimetic activity ISA. - Has membrane stabilizing effects.	- Lipophilic.	- Hypertension. - Anxiety (specially social & performance type). - Migraine (Prophylaxis). - Cardiac arrhythmia. - Myocardial infarction. - Hyperthyroidism (Thyrotoxicosis).	-
Timolol	- Non-selective β1 & β2. - Without ISA.	- Lipophilic.	- Chronic glaucoma as eye drops.	-
Atenolol	- Selective-β1 antagonist. - Without ISA.	-	- Hypertension. - Cardiac arrhythmia. - Myocardial infarction.	-
Bisoprolol		-	- Hypertension. - Cardiac arrhythmias (preferred). - Hyperthyroidism -Congestive heart failure	-
Metoprolol		- Lipophilic.	- Hypertension. - Myocardial infarction. -Congestive heart failure	-
Esmolol	- Selective-β1 antagonist.	- Half life: 10min (ultra-short acting). - I.V. .	- Cardiac arrhythmia.	-
Carvedilol	- Non-selective blocks α & β. - No ISA and local anesthetic effect. -Has ANTIOXIDANT action.	- Lipophilic.	- Used effectively in Congestive heart failure. - Cardiac arrhythmias (preferred). - Hypertensive emergency.	- Orthostatic hypotension. - Edema.
Labetalol	- Non-selective blocks α & β. - Has ISA. - Has membrane stabilizing effects. -local anesthetic effect	- Lipophilic. - Given p.o and I.V. .	- Severe hypertension in pheochromocytoma. - Hypertensive crisis (e.g. during abrupt withdrawal of clonidine). - Used in pregnancy-induced hypertension.	- Orthostatic hypotension. - sedation. - dizziness.

Anti-Arrhythmic drugs

Class I

Na+ channel blocker (membrane stabilizing drugs)

Subclass: IA

(Prolong action potential duration)

Drug	M.O.A	Clinical uses	Adm	ADRs
Quinidine	**1/Anticholinergic effects** -Increase conduction through the A.V node (risk of ventricular tachycardia) **2/α-adrenergic blocking effect** -May cause vasodilation and reflex tachycardia (seen more after I.V dose) **3/ECG changes:** **-**Prolongs P-R & Q-T interval -Widens QRS complex	-Atrial flutter & fibrillation -Maintaining sinus rhythm after cardioversion.	Given Orally (Rarely given I.V)	1- Quinidine syncope: -Episodes of fainting due to torsades de pointes developing at therapeutic plasma levels 2- Anticholinergic adverse effects: Dry mouth, Blurred vision, Urinary retention, N/V/D & constipation 3-Hypotension: Due to depressing contractility
Procainamide	**Similar to Quinidine except:** 1/Less toxic on the heart 2/More effective in ventricular than in atrial arrhythmias 3/Less anticholinergic or α-blocking actions	More effective in ventricular than in atrial arrhythmias.	I.V	1- In long term therapy it causes reversible lupus erythematosus like syndrome. 2- **Hypotension**. 3- **Torsades de pointes** (At toxic dose) 4- Hallucination & psychosis

Subclass: IB

(Shorten action potential duration)

Drug	M.O.A	Clinical uses	Adm	ADRs
Lidocaine	Na+ channel blocker	1/Treatment of emergency **ventricular** arrhythmias e.g: 1-During surgery 2-Following acute myocardial infarction. (NOT effective in **atrial** arrhythmias)	Given I.V. bolus or slow infusion. (NOT effective orally due to only 3% bioavailability)	1-Hypotension 2-CNS ADRs -Paresthesia -Tremor -Dysarthria (slurred speech) -Tinnitus -Confusion -Convulsion
Mexiletine		1/ventricular arrhythmias 2/Digitalis-induced-arrhythmia	Effective Orally	1- nausea, vomiting 2- tremor, drowsiness,diplopia 3- arrhythmias & hypotension

Anti-Arrhythmic drugs

Subclass: **IC**
(No effect on action potential duration)

Drug	M.O.A	Clinical uses	Adm	ADRs
Flecainide	Block the influx of Na Ions (markedly slow phase 0 depolarization)	1/Supraventricular arrhythmias 2/Wolff-Parkinson-White syndrome (WPW) 3/Very effective in ventricular arrhythmias, **but very high risk of proarrhythmia** 4/Should be reserved for resistant arrhythmias.	-	1/Proarrhythmia 2- CNS : dizziness , tremor, blurred vision, abnormal taste sensations, paraesthesia. 3- Heart failure due to -ve inotropic effect

Class II

Drug	Mechanism of action	Clinical uses	
Esmolol	block β_1 receptors in the heart → Reduce sympathetic effect on the heart which leads to: 1- ↓ automaticity of S.A. node & ectopic pacemakers 2-prolong RP (refractory period) (slow conduction) of the A.V node	1- atrial arrhythmias associated with emotions e.g.: (after exercise , thyrotoxicosis) 2- WPW 3- Digitalis induced arrhythmias	- given I.V. for rapid control of ventricular rate in patients with atrial flutter or fibrillation -Very short acting (t1/2 = 9 min)
Propranolol , Atenolol, metoprolol			-Used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias

Anti-Arrhythmic drugs

Class III

Amiodarone (prototype)

Pharmacologica Action	**Main effect:** 1- prolong action potential duration and prolong refractory period 2- Prolong phase 3 repolarization Additional effect: -Class IA - Class II - Class IV -**Vasodilating effects** (due to its α & β-adrenoceptor blocking effects and its calcium channel blocking effects)
P.K	-Extremely long half-life (13 - 103 DAYS) -Metabolized by (CYP3A4 and CYP2C8) to its major active metabolite ; N-desethylamiodarone -Eliminated primarily by hepatic metabolism -Can cross placenta, and appear in breast milk
Clinical Use	-**Main use**: serious resistant ventricular arrhythmias. -Maintenance of sinus rhythm after. cardioversion -Resistant supraventricular arrhythmias e.g. WPW
ADR's	-Exacerbation of ventricular arrhythmias (high dose) -**Bradycardia** and heart failure -**Pulmonary fibrosis** -**Hyper or hypothyroidism**)-**Photodermatitis** & **skin deposits** (patients should avoid exposure to the sun) -Neurological (e.g. tremors and peripheral neuropathy) -Nausea, vomiting and constipation -**Corneal micro deposits** -**Hepatocellular necrosis**

Drug Interactions	**(pharmacodynamics)**	**(pharmacokinetic)**	**(pharmacokinetic)**
	Co-administration of amiodarone with drugs that prolong the QT interval increases the risk of Torsades de Pointes E.g. 1-Macrolides : Clarithromycin & Erythromycin 2- Azole antifungals Ketoconazole	Drugs (or substances) that inhibit CYP3A4 & CYP2C8 enzymes cause increase in serum concentration of amiodarone **e.g.** Loratadine, Ritonavir Trazodone, Cimetidine, Grapefruit juice	Drugs that induce these enzymes Cause decrease in serum concentration of amiodarone **e.g**. Rifampin

Anti-Arrhythmic drugs

Class III

Ibutilide (Pure Class III)

M.O.A	Pharmacological action	Administration	Clinica Use	ADR's
Prolong the action potential duration & RP Prolong phase 3 repolarization	Causes QT interval prolongation (phase 3)	Given by rapid I.V. infusion	Used for acute conversion of atrial flutter Atrium or fibrillation to normal sinus rhythm	May cause Torsades De Pointes

Class IV

Verapamil , Diltiazem

M.O.A & Pharmacological Action	Clinical Use
-Calcium channel blockers. -Main site of action is S.A & A.V nodes, causes -Slowing of conduction -Prolongation of (**ERP**)	-Atrial arrhythmias -Re-entry supraventricular arrhythmias (e.g. WPW) (NOT effective in ventricular arrhythmia)

Class V

Miscellaneous Antiarrhythmic Drug

Adenosine

M.O.A	Pharmacokinetics	Therapeutic uses	ADR's
Inhibit **cAMP** by binding to adenosine A1 receptors causing the following actions : 1- Opening of potassium channels (Hyperpolarization) 2-Decreasing conduction velocity , mainly at AV node (-ve dromotropic effect) and chronotropic effect 3- Inhibiting phase 4 pacemaker M.O.A action potential at SA node (-ve chronotropic effect)	Half-life is less than 10 sec	Drug of choice for acute management of paroxysmal supraventricular tachycardia preferred over verapamil (because it's safer and does not depress contractility)	-Flushing (in about 20% of patients) -Shortness of breath & chest burning (in 10% of patients) due to bronchospasm -Brief A.V block (Contraindicated in heart block)

Anti-Arrhythmic drugs

New Antiarrhythmic Drugs

Drug	M.O.A	Clinical uses
Dronedarone	**Pharmacological Action:** It has antiarrhythmic properties belonging to all four classes **Contraindications**: -Should NOT be used in patients with severe (class IV) heart failure. (Risk of death may be increased in these patients) Contraindications -Should NOT be used in patients with permanent atrial fibrillation. (Risk of death and stroke may be increased in these patients)	maintenance of sinus rhythm following cardioversion in patients with atrial fibrillation

Bradyarrhythmias

Drug	M.O.A	Clinical uses
Atropine	-	-Used in sinus bradycardia after myocardial infarction and in heart block -In emergency heart block isoprenaline may be combined with atropine (caution)

Drug Therapy of Heart Failure

Drug that decrease Preload

Class	Drug	MOA	P.K	Use	ADRs	Contraindications
Diuretics	**Chlorothiazide** (Thiazides)	Decrease salt and water retention (↑excretion) ⟶ decrease ventricular preload & venous pressure ⟶ reduction of cardiac size ⟶ Improvement of cardiac performance.	-	-First-line agent in HF therapy -Mild CHF -Volume overload	-hypotension -hypokalemia. - increase urine output	-
	Furosemide (Loop)		-	-immediate reduction of pulmonary congestion & severe edema associated with: AHF, Moderate & severe chronic failure.		-
Aldosterone antagonists	**Spironolactone**	-Potassium sparing diuretic -Non-selective Antagonist of aldosterone receptor.	-	Improves survival in advanced HF	-	-
	Eplerenone	-selective aldosterone receptor Antagonist (does not inhibit other hormones; estrogens & androgens).	-	Improves survival of stable patients with CHF	-	-
Venodilators	**Nitroglycerine**	↑cGMP in smooth muscles of vessels⟶ Dilates venous blood vessels & reduce preload.	I.V for severe cases	severe HF when the main symptom is dyspnea due to pulmonary congestion.	-	-
	Isosorbide dinitrate					

Drugs that decrease afterload

Class	Drug	MOA	P.K	Use	ADRs	Contraindications
Arteriodilators	**Hydralazine**	reduce peripheral vascular resistance.	-	when the main symptom is rapid fatigue due to low cardiac output.	lupus-like-syndrome	–

Drugs that decrease both preload & afterload

Class	Drug	MOA	P.K	Use	ADRs	Contraindications
ACEI	**Captopril** **Enalapril** **Ramipril**	1-inhibiting ACE, we will achieve the opposite of all angiotensin II normal actions: -Decrease preload & afterload -Decrease sympathetic activity -Inhibit remodeling 2-Accumulation of Bradykinin: -vasodilatation 3-Decrease mortality rate	-Rapidly absorbed from GIT after oral administration - Food reduce their bioavailability. ——————— -Prodrugs, activated in liver -long half-life -given once daily. (only Enalapril & Ramipril)	-first-line drugs for chronic heart failure (along with diuretics) -first-line treatment HTN	-Acute renal failure -Hyperkalemia -Dysgeusia -Dry cough -Angioneurotic edema -Severe hypotension in hypovolemic patients (Due to diuretics, salt restriction, fluid loss)	-2nd & 3rd trimesters of pregnancy (risk of : fetal hypotension, renal failure and malformations). -Renal artery stenosis.
ARBs	**Losartan** **Valsartan** **Irbesartan**	-Block angiotensin 1 (AT1) receptors -Decrease action of angiotensin II.	-	-	-	–
α-Adrenoceptor Blockers	**Prazosin**	- blocks α- receptors in arterioles and venules. - decrease afterload & preload.	-	-	-	–
Direct acting vasodilators	**Sodium nitroprusside**	by ↑ cGMP	-Acts immediately -effects lasts for 1-5 min.	- Given I.V In acute or severe heart failure	-	–

Drug Therapy of Heart Failure

Drugs that increase contractility

Class	Drug	MOA	Uses	ADRs	Interactions
Cardiac glycosides (digitalis)	**Digoxin**	-Inhibit Na+ / K+ ATPase enzyme (the sodium pump) -Increases the force of myocardial contraction	-CHF -Has Narrow T.I	-digitalis-induced arrhythmias: .Bigeminal beats (Rythm) .Extrasystoles .Ventricular tachycardia .fibrillation .Cardiac arrest -GIT manifestations -CNS disturbances	Factors that increase its toxicity: -Renal diseases -Hypokalemia -Hypomagnesemia -Hypercalcemia
β-Adrenoreceptor AGONIST	**Dobutamine**	Selective β1 agonist	Treatment of acute heart failure in cardiogenic shock	-	-
phosphodiesterase-III inhibitors	**Milrinone**	-Inhibits PDE-III (cardiomyocytes & vascular smooth muscle) ⟶ ↑cAMP. . in cardiomyocytes⟶ Increases cardiac contractility. . in vascular smooth muscles⟶ Dilatation of arteries & veins (reduction of preload & afterload).	-only IV for management of AHF. -Not safe or effective in longer than 48 hrs of treatment	-Hypotension -chest pain (angina).	**Furosemide** should not be administered in I.V. lines containing milrinone due to formation a precipitate.
	Enoximone **Vesnarinone**		New drugs in clinical trials	-	-

Other drugs for heart failure

β-adrenoreceptor blockers	**Bisoprolol** **Metoprolol** (Second generation)	-Attenuate cardiac remodeling. -Slow HR - Decrease renin release -reduce mortality & morbidity of patients with HF	-Reduce the progression of CHRONIC heart failure. -NOT used in ACUTE heart failure.	-	-
	Carvedilol **Nebivolol** (Third generation)			-	-
Natriuretic Peptides (New drug for HF)	**Nesiritide**	-Physiological effects of ANP and BNP -↑ Cyclic-GMP in vascular smooth muscle leading to : . vasodilation . Reduction of preload & afterload.	Indicated (IV) for the treatment of patients with ADHF who have dyspnea at rest or with minimal activity	-	-
Calcium sensitisers (New drug for HF)	**Levosimendan**	-Calcium sensitization: .improves cardiac contractility WITHOUT increasing oxygen consumption. -Potassium-ATP channel opening: .vasodilation .improving blood flow to vital organs	management of ADHF	-	-

Anti-hypertensive drugs

Diuretics

Drug	(Thiazides) Hydrochlorothiazide chlorothiazide chlorthalidone	(Loop Diuretics) Furosemide	(Potassium-sparing Diuretics) Spironolactone
Uses	Their action may differ between the short and long use	Hypertension with **renal impairment** Manage symptoms of **H.F** and edema	Minimal effect on lowering BP
	Mild to moderate Hypertension		
M.O.A	The initial diuresis lasts 4-6 weeks and then replaced by a decrease in the PVR (Peripheral vascular resistance).		

Vasodilators

Drug	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Uses	Moderate-severe hypertension		Hypertensive emergency	
M.O.A	Direct	Opening of potassium channels in smooth muscle membrane by minoxidil sulfate	Opening of potassium channels	Release of (NO)
Administration	Oral		Rapid I.V	I.V infusion
Site of action	Artiodilator			Arterio & venodilator
Uses In combination with a diuretic & first-line. β-blockers	Hypertensive pregnant woman	Correction of baldness	Treat hypoglycemia due to Insulinoma	Severe heart failure
ADRs	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema).			Severe hypotension
Specific ADRs	lupus erythematosus like syndrome	Hypertrichosis thus contraindicated in females	Inhibit insulin release from β cells of the pancreas causing hyperglycemia. contraindicated in diabetics	Methemoglobin during Infusion - Cyanide toxicity - Thiocyanate toxicity - Headache, palpitations which disappear when infusion is stopped. - Cyanide accumulation cause cyanide poisoning (metabolic acidosis, arrhythmias, severe hypotension and death)

Anti-hypertensive drugs

Angiotensin Converting enzyme inhibitors (ACEIs)

Drugs	**Captopril, Lisinopril, Enalapril, Ramipril**
M.O.A	● Particularly effective when hypertension results from excess renin production (renovascular hypertension, white & young) ● ACE inhibitors decrease angiotensin II and increase bradykinin levels by preventing its degradation by ACE , so the antihypertensive effect results primarily from vasodilatation with little change in CO. ● A fall in aldosterone production may also contribute.
P.K	-Polar, excreted in urine. -Do not cross BBB -Have a long half life & given once daily. -Rapidly absorbed from GIT after oral administration. -Food reduce their bioavailability. -It takes 2-4 weeks to notice the full antihypertensive effect of ACEIs. -Enalapril & Ramipril are prodrugs, converted to the active metabolite in the liver. -Enalaprilat is the active metabolite of Enalapril, can be given by I.V. route in hypertensive emergency.
Uses	-Treatment of essential hypertension. -Hypertension in patient with chronic renal disease, ischemic heart disease , diabetes. -Treatment of Heart failure.
ADRs	-Dry Cough -Acute renal failure, especially in patients with renal artery stenosis. -Severe hypotension in hypovolemic patients -Renal angensia/ failure in the fetus resulting in oligohydramnios -Angioneurotic edema (swelling in nose, tongue, throat & larynx) . -First dose effect (severe hypotension) (Given at bed time - start with small dose and increase the dose gradually) -Adverse effects Specific to captopril ➔ skin rash, fever, dysgeusia,Proteinuria and neutropenia. These effects are due to a sulfhydryl group in the molecule of captopril.
Contraindication	-During the second and third trimesters of Pregnancy due to the risk of; fetal hypotension, anuria, renal failure & malformations. -Renal artery stenosis. -Potassium-sparing diuretics. -Patients using NSAIDs .

Anti-hypertensive drugs

Angiotensin receptors blockers (ARBs)

Drugs	Losartan	Valsartan	Candesartan Telmisartan
P.K	-Has a Potent active metabolite. -Effective Orally once daily. -long half life. -Do not cross BBB.	No active metabolite	-
M.O.A	- selective block of AT1 receptors. - No effect on bradykinin, no cough, no angioedema. - Produce more complete inhibition of angiotensin than ACE inhibitors		
ADRs	Same as ACEI except dry cough & angioneurotic edema.		
contraindication	Same contraindications as ACEI .		

Calcium channel blockers

Class	Phenylalkylamine	Dihydropyridine	Benzothiazepine
Drug	Verapamil	Nifedipine	Diltiazem
Feature	Act mainly on myocardium	Act more on smooth muscle	intermediate effect
M.O.A	Block the influx of calcium through calcium channels resulting in: 1- Peripheral vasodilatation. 2- Decrease cardiac contractility.		
P.K	given orally (onset: 0.5-2h) and I.V. injection (onset 1-3min), well absorbed. ● Verapamil & diltiazem have active metabolites, nifedipine has not. ● Verapamil and nifedipine are highly bound to plasma proteins (more than 90%) while diltiazem is less Bound (70-80%) ● Sustained-release preparations can permit once-daily dosing.		
Uses	Treatment of chronic hypertension. especially for Nifedipine. ● Nicardipine can be given by I.V. route & used in hypertensive Emergency. ● Sustained-release formulations are preferred for the treatment of hypertension due to the short half- life of CCBs.		
ADRs	peripheral edema (ankle edema) - constipation	Tachycardia	Peripheral edema (ankle edema)
	Headache , Flushing , Hypotension		

Anti-hypertensive drugs

Sympatholytic drugs

	Drugs	Uses	M.O.A	ADRs	
B-adrenoceptor blockers	**propranolol** (Non selective)	used in mild to moderate hypertension In severe cases used in combination with other drugs -therapeutic response may take up to two weeks -evidence support their use in patient with coronary heart disease -when discontinued should be withdrawn gradually	1- decrease cardiac output 2- inhibit renin release 3- Centrally mechanism	-Aggravate peripheral arterial disease -hypoglycemia -increase triglycerides -erectile dysfunction	-mask hypoglycemia symptoms in diabetics (don't use with diabetics patients) -Fatigue
	atenolol (Selective beta 1 blocker)			bradycardia,hypotension	
	metoprolol (Selective beta 1 blocker)				
α- adrenoceptor blockers	**prazosin** (Short acting)	benign prostatic hypertrophy	-blocks alpha 1 receptors in arterioles and venules - reducing blood pressure by decreasing preload and afterload	Causes first dose hypotension and postural hypotension	
	doxazosin (Prefered for its long half life)			-	
centrally acting sympatholytic drugs	**Clonidine** (Direct α2-agonist)	-hypertension with renal disease -Resistance hypertension	Diminish central adrenergic outflow from the CNS & increase parasympathetic outflow to the heart. This leads to reduced total peripheral resistance and decrease BP.	Abrupt Sudden withdrawal of clonidine can lead to rebound hypertension.	
	α-methyldopa (Indirect α2-agonist)	α -Methyldopa is the first line treatment of hypertension in pregnancy		-	

Thrombolytic Drugs

Non Fibrin specific thrombolytic drugs)

	Streptokinase (SK)	Anistreplase (APSAC)	Urokinase
M.O.A	- Is a bacterial protein produced by B-hemolytic streptococci. - It acts **indirectly** by forming plasminogen-streptokinase complex M.O.A "**activator complex**" which converts inactive plasminogen into active plasmin. - Can degrade **fibrin clots** as well as **fibrinogen** and other plasma proteins.	- **(APSAC)** : **A**nisoylated **P**lasminogen **S**treptokinase **A**ctivator **C**omplex is an acylated plasminogen combined with streptokinase. - It is a **prodrug** , de-acylated in circulation into the active plasminogen-streptokinase complex. -direct	- Human enzyme synthesized by the kidney - Obtained from either urine or cultures of human embryonic kidney cells. - Is a **direct** plasminogen activator.
T 1/2	**Less than 20 minutes**	**70-120 minutes**	**12-20 minutes**
Administration	**I.V** infusion	**Bolus I.V**. Injection	**I.V** infusion
Advantages	- Least expensive. - Used for **venous** and **arterial** thrombosis.	- Longer duration of action than streptokinase. - More thrombolytic activity. - Greater clot selectivity.	- Used for the lyses of acute massive pulmonary emboli - No anaphylaxis (not antigenic).
Disadvantages & side effects	1- **Antigenicity** : high-titer antibodies develop 1 to 2 weeks after use, precluding retreatment until the titer declines. 2- **Allergic reaction :** like rashes, fever, hypotension. 3- **Bleeding** due to activation of circulating plasminogen (systemic fibrinolysis). 4- Not fibrin specific.	**Similar but less than streptokinase alone in:** - Antigenicity. - Allergic reactions. - Minimal fibrin specificity - Systemic lysis/hemorrhage More **expensive than streptokinase**	-Minimal fibrin specificity -Systemic lysis (acts upon fibrin-bound and circulating plasminogen). - Expensive (its use is now limited).
Precautions	**Not used in patients with:** - Recent streptococcal infections. - Previous administration of the drug * These patients may develop fever, allergic reactions and resistance upon treatment with streptokinase due to antistreptococcal antibodies.*	-	

Thrombolytic Drugs

Fibrin specific thrombolytic drugs

Tissue Plasminogen Activators (t-PAs)

Drug	Alteplase	Reteplase	Tenecteplase
M.O.A	- All are recombinant human tissue plasminogen activators (tPA). - Prepared by recombinant DNA technology. **Directly act by:** - They activate **fibrin-bound plasminogen** rather than free plasminogen in blood - Their action is **enhanced by the presence of fibrin**. - They bind to fibrin in a thrombus and convert the entrapped plasminogen to plasmin followed by activated local fibrinolysis with **limited systemic fibrinolysis** .		
T 1/2	**5 minutes (short)**	**15 minutes (longer)**	**30 minutes (longest)**
Administration	**Bolus I.V**. Injection followed by infusion	**Two I.V**. **Bolus** Injection	Single **I.V bolus** injection
Advantages	1. Fibrin-specific drugs (clot specific). 2. Limited systemic fibrinolysis. 3. Reduced risk of bleeding 4. Not-antigenic (can be used in patients with recent streptococcal infections or antistreptococcal antibodies).		
Specificity	-	**Has Enhanced fibrin specificity**	**It is more fibrin specific**
Uses	**-In ST-elevation myocardial infarction (STEMI) .** **-Pulmonary embolism .**		**It is only approved for use in acute myocardial infarction .**

Fibrinolytic Inhibitors (Antiplasmin) : inhibit plasminogen activation & inhibit fibrinolysis & promote clot stabilization

Drug	Aminocaproic Acid & Tranexamic acid	Aprotinin
M.O.A	Acts by competitive inhibition of plasminogen activation	It inhibits fibrinolysis by blocking the action of plasmin (plasmin antagonist)
Administration	**Orally**	**Orally or I.V**
Uses	- Fibrinolytic therapy induced bleeding (antidote). - Post surgical bleeding. - Adjuvant therapy in hemophilia. - These drugs work like antidotes for fibrinolytic drugs. Similar to Protamine (antidote of anticoagulant, heparin) or Vitamin K (antidote of the oral anticoagulant, warfarin)	

Anti-Anginal Drugs

Agents that improve symptoms and ischemia: (Traditional Approaches)

1.Organic Nitrates

Drug	Nitroglycerine (GTN) Short acting	Isosorbide mononitrate & dinitrate Long acting
P.K	·Given sublingual or transdermal patch or parenteral. · Can't be given orally, because it goes through Significant first pass metabolism in the liver · Only (10-20%) bioavailability if given orally	· Very well absorbed . Mononitrate, 100% bioavailability · The dinitrate undergoes denitration in liver to two mononitrates ➜ both possess antianginal activity which then conjugate to glucuronic acid in liver. · T1/2= 1-3 hours. · Excreted in urine.
Main use	· Rapid for terminating an acute attack of stable angina.	· For long-term persistent prophylaxis of stable angina.
Indications	IN STABLE ANGINA: ● Acute symptom relief ➜sublingual GTN ● Prevention; Situational prophylaxis➜sublingual GTN IN VARIANT ANGINA➜ sublingual GTN IN UNSTABLE ANGINA IV GTN ● Heart failure ● Refractory AHF1 ➜IV GTN ● AMI2➜IV GTN	IN STABLE ANGINA: ● Prevention; Persistent prophylaxis ➜Isosorbide mono or dinitrate. IN UNSTABLE ANGINA: ● CHF3➜ Isosorbide mononitrate + hydralazine [if contraindication to ACE Is used]
Preparation	● Sublingual tablets or spray Have rapid onset of action and short duration (30min), ● Transdermal patch(8-14h) ● Oral or bucal sustained release ● I.V. Preparations	● Dinitrate Sublingual tablets ● Dinitrate Oral sustained release ●Mononitrate Oral sustained release ● Infusion Preparations
mechanism	1. Release NO through interactions with intracellular SH groups and with further enzymatic degradation, NO is produced. Nitric oxide then binds to guanylate cyclase in vascular smooth muscle cell to form cGMP. 2. cGMP activates PKG (Protein Kinase G) to produce relaxation	
Contra-indications	1. Known sensitivity to organic nitrates. 2. Glaucoma. nitrates increase synthesis of aqueous humor 3. Head trauma or cerebral haemorrhage 4. Uncorrected hypovolemia 5. Concomitant administration of PDE5 Inhibitors. Sildenafil + nitrates ➞ Severe hypotension & death	
ADRS	1. Reflex tachycardia and palpitation 2. Throbbing headache 3. Flushing of blush area 4. Postural hypotension, Dizziness and Syncope 5. Rarely Methemoglobinemia	

2. Calcium channel blockers

Class - Drug	Dihydropyridine - Nifedipine - Amlodipine - Nicardipine	Phenylalkylamine Verapamil	Benzothiazepine Diltiazem
Selectivity	Dihydropyridine group act mainly on Vascular smooth muscle.	Act more on myocardium.	Has intermediate effect.
M.O.A	Calcium channel blockers ➞Bind to L Type Ca channels (Dr's note: the most important type, involved in anginal pain) ➞ decrease their frequency of opening in response to depolarization ➞ ↓ entry of Ca ➞ ↓ Ca release from internal stores(sarcoplasmic reticulum) ➞ No Stimulus-Contraction Coupling ➞ RELAXATION		
P.D Antianginal actions	2-Dihydropyridines ↓ VSMC(vascular smooth muscle cell) Contraction ➞ arteriolar vasodilation ↓ Afterload ➞ ↓ cardiac work ➞ ↓myocardial oxygen demand	1-verapamil & diltiazem ↓ Cardiomyocyte Contraction ➞ ↓ cardiac work through their –ve inotropic & chronotropic action ➞ ↓ myocardial oxygen demand	
	3-coronary dilatation ↑ myocardial oxygen supply		
Indications in angina	Stable Unstable Variant	Regular prophylaxis. Seldom (rarely) added in refractory cases. Attacks are prevented (>60%)/sometimes variably aborted (stops pain)	

Anti-Anginal Drugs

3. β1 Selective blockers

Drug	Atenolol	Bisoprolol	Metoprolol
P.D	Acts on cardiomyocyte: 1. Negative inotropic effect (force of contraction) ↓cardiac work →↓ myocardial oxygen demand 2. Negative chronotropic effect (Heart rate = bradycardia) Increase diastolic duration Due to the bradycardia(give time for filling) → Increase coronary blood flow →↑ myocardial oxygen supply		
Indications as antianginal	Stable	1. Cardioselective (beta 1 blockers) are preferred to avoid affecting lung (bronchiole) and blood vessels 2. First choice for Chronic use with nitrate.	
	Unstable	halts (stops) progression to MI, improve survival	
	Variant	Contraindicated, because they are ineffective and may actually worsen symptoms.	
Indications as acute Myocardial infarction	Given early to ↓ Infarct size, morbidity & mortality (↓ incidence of sudden death) ↓Arrhythmia and ↓ O2 demand		

Agents that improve symptoms and ischemia: (New Approaches)

1-Potassium Channel Openers

Drug	Nicorandil	
P.D Dual mechanism	1. Opening of KATP channels	2. Acting as NO donor
	On VSMCs :K+ channel opening → Hyperpolarization → VASODILATATION (Improves coronary blood flow)	On VSMCs: NO donner → increase cGMP/ PKG → VASODILATATION
	On Cardiomyocyte : K channel opening Repolarization → relaxation of myocardial cells → ↓ Cardiac work	
Indications	1. Prophylactic 2nd line therapy in stable angina. 2. Refractory (not responding) variant angina if not responding to nitrate and CCB.	
ADRs	Flushing, headache, Hypotension, palpitation due to nitrate effect Weakness, Mouth & peri-anal ulcers Dr's note:special ADR for nicorandil , nausea and vomiting	

Anti-Anginal Drugs

2- Metabolically Acting Agents

Drug	Trimetazidine
P.D Dual mechanism	During ischemia, metabolism shifts to oxidation of FFA (fatty acids), which provides more energy but requires more O2 than Glucose utilization. So, to decrease O2 consumption & demand, we can enhance utilization of glucose (less O2 requirement) by giving Partial FFA Oxidation Inhibitors (e.g. Trimetazidine)
Indications	Used as an add on therapy
ADRs	GIT disturbances
Contraindications	·Hypersensitivity reaction ·In pregnancy & lactation

3-.Late Na+ current inhibition

Drug	Ranolazine
Pharmaco-logical effect	·Inhibits the late sodium current(which opens in phase 4 depolarization), which increases during ischemia and affects Na dependent-Ca Channels.
Indications	Used in chronic angina concomitantly with other drugs
ADRs	GIT disturbances
Precautions	·It prolongs the QT interval so contraindicated with Class Ia & III antiarrhythmic drugs . ·Toxicity develops due to interaction with CYT-p450 inhibitors as; diltiazem, verapamil, ketoconazole, macrolide antibiotics, grapefruit juice

4-Sinus node inhibition

Drug	Ivabradine
M.O.A	-Selectively blocks I_f (I_f current is an inward Na+/K+ current that activates pacemaker cells of the SA node)
Pharmacodynamic effect	-Acts on the " Funny Channel" a special Na channel in SAN, reduces slope of depolarization, slowing HR, reducing myocardial work & Myocardial O2 demand
Indication	-Used in treatment of chronic stable angina in patients with normal sinus rhythm who cannot take ß-blockers. -Used in combination with beta blockers in people with heart failure with LVEF lower than 35 percent inadequately controlled by beta blockers alone and whose heart rate exceeds 70/min
ADRs	luminous phenomena

Drugs for hyperlipidemia

Hypolipidemics can be divided into five categories: 1-statins, 2- fibric acid derivatives, 3-niacin , 4-resins 5- cholesterol absorption inhibitors (ezetimibe).

Bile acid sequestrants/ Resins

Drug	MOA	Uses	ARDs	Contraindication	Drug interactions
Cholestyramine	- Bind to bile acids in the small intestine & **form insoluble complex.** This complex cannot be reabsorbed from the intestine. - The liver increases the number of LDL receptors to obtain more cholesterol and to convert it to bile salts , thus, the levels of LDL in the serum are reduced.	second -line therapy for hypercholesterolemia	- GIT upset: abdominal discomfort, bloating, constipation. - Decreased absorption of fat soluble vitamins (A, D, K).	hypertriglyceridemia (TG >400 mg/dL).	Interfere with the absorption of many drugs. Therefore, other drugs should be taken 1 hour before, or 4 hours after taking resins. **Except colesevelam,** it has not been shown to interfere with the absorption of other drugs
Colestipol					
Colesevelam					

Cholesterol Absorption Inhibitors

Drug	MOA	Uses	ARDs	Contraindication	Drug interactions
Ezetimibe	Inhibits intestinal cholesterol absorption by **inhibiting Niemann-Pick C1-like 1 (NPC1L1) receptor**→ ↓delivery of dietary cholesterol to the liver. ↑upregulation of LDL receptor → trapping more LDL particles from blood. Results in ↓ total cholesterol and LDL with minimal effects on HDL and triglycerides.	Hypercholesterolemia. Usually used in conjunction with a statin (synergistic effect).	Not common But may occur: GIT disturbance, headache, fatigue, arthralgia and myalgia	-	-

Drugs for hyperlipidemia

Hypolipidemics can be divided into five categories: 1-statins, 2- fibric acid derivatives, 3-niacin , 4-resins 5- cholesterol absorption inhibitors (ezetimibe).

Statins

(Rosuva**statin ,**Atorva**statin,** Lova**statin,** Prava**statin,** Simva**statin,** fluva**statin)**

MOA	P.K	Uses	ARDs	Contra-indication	Drug interactions
HMG-CoA reductase inhibitor. Blocks endogenous cholesterol synthesis, forcing hepatocytes to ↑LDL receptors → ↑ hepatic LDL catabolism and LDL precursor extraction (VLDL remnants) from the circulation. Results in large ↓ in total cholesterol and LDL, medium ↓ in triglycerides, and small ↑ in HDL.	PO. Metabolized by **CYP3A4.** Taken at bedtime because of hepatic C synthesis is maximal between midnight & 2:00 am. Except atorvastatin taken at any time because of its long T½ (14 hrs).	First-line therapy to **reduce hypercholesterolemia & LDL levels** in patients at risk for or with coronary artery disease. Used In diabetics and patients with insulin resistance. Reduces cardiovascular mortality and risk of myocardial infarction, and stroke	- Common side effects: Headache, **myalgia** ,fatigue, GI intolerance and flu-like symptoms. -Hepatotoxicity ↑concentration of serum aminotransferases. - Myopathy ↑[CK] -Teratogenicity	-Pregnancy -liver disease	- **Fibrates** (↑ risk of myopathy). - Drugs metabolized by 3A4 isoform of cytochrome P450 like: erythromycin, verapamil ,cyclosporine, ketoconazole. Except **pravastatin** & **fluvastatin ,** these are the statin of choice in patients taking other drugs metabolized by CYP3A4 system

Niacin

MOA	Uses	ARDs	Contra-indication	Drug interactions
Inhibits hormone-sensitive lipase in adipose tissue → ↓**lipolysis of triglycerides** → ↓transport of free fatty acids to the liver and ↓**hepatic synthesis of triglycerides.** Reduction of triglyceride synthesis reduces hepatic VLDL synthesis → ↓ LDL. ↑ peripheral lipoprotein lipase activity → improved VLDL clearance and ↓ TG. ↓ apo-A-I clearance → ↓ HDL catabolism. Promotes hepatic apoAI production Results in large ↓ in triglycerides, medium ↑ in HDL, and medium ↓ in total cholesterol and LDL.	- Hypercholesterolemia with concomitant hypertriglyceridemia. Used in patients with low HDL levels	- Flushing (which is prostaglandin mediated) can be avoided by low dose Aspirin ½ hour before niacin and by using sustained-release preparations. - GI distress: reactivation of peptic ulcer (can be↓ if taken after meal) - glucose intolerance → overt diabetes -Impairment of glucose tolerance → overt diabetes -↑ uric acid → gout.	- Gout - Peptic ulcer - Hepato-toxicity - Diabetes mellitus (used with caution)	-

Drugs for hyperlipidemia

Hypolipidemics can be divided into five categories: 1-statins, 2- fibric acid derivatives, 3-niacin , 4-resins 5- cholesterol absorption inhibitors (ezetimibe).

Fibrates
(fibric acid derivatives)

Drug	MOA	Uses	ARDs	Contraindication	Drug interactions
Clofibrate **Gemfibrozil** **Fenofibrate**	binds to and activates nuclear peroxisome proliferator activated receptor- (PPARα), expressed primarily in the liver and skeletal muscle. These receptors increase gene transcription of **lipoprotein lipase (LPL)** leading to increased catabolism of TG in VLDL and chylomicrons. They cause : ● A marked reduction in TG (due to catabolism of VLDL). ● ↑FFA uptake by the liver ● ↑LDL-C uptake by the liver. ●↑ HDL by ↑ apoA-I and apoA-II expression. ● ↑ excretion of hepatic C in bile, thus endogenous hepatic C synthesis may be decreased. Results in large ↓ in triglycerides, medium ↑ in HDL, and small ↓ in total cholesterol and LDL.	●Hypertriglyceridemia **1st-line defense for:** ● mixed dyslipidemia (i.e. raised serum TG and C). ● Low HDL levels. (Improves clinical outcomes in patients with coronary disease and low HDL levels.) ● Patients with resistant dyslipidemia	GI distress, rash, myopathy, gallstones.	-Severe hepatic or renal dysfunction. -Pregnant or nursing women.	● Increased risk of myopathies when used with statins (they ↓metabolism of statins, so must be given in low doses) ● Potentiates effects of anticoagulant like warfarin & oral hypoglycemic drugs (because they displace drugs from plasma proteins (oral).

GOOD LUCK!

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