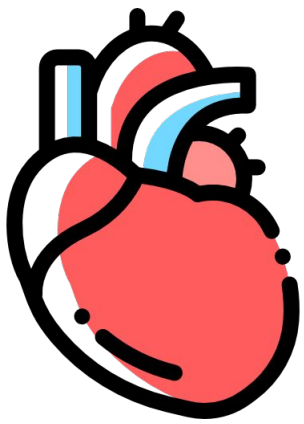
MED441
KING SAUD UNIVERSITY

Cardiovascular Block Summary

Pharmacology
TEAM 441

اللهم إني أسألك فهم النبيين، وحفظ المرسلين، والملائكة المقربين،
اللهم اجعل ألسنتنا عامرة بذكرك، وقلوبنا بخشيتك، وأسرارنا بطاعتك،
إنك على كل شيء قدير



Pharma Flashcards **here**
Thank you #439

Editing file

#1. Sympatholytic & adrenergic blockers α-receptor Antagonists

Classification	Drug	MOA	Uses	Adverse effect	Contraindication
Adrenergic Neuron Blockers	**α-Methyl dopa**	-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	
	Apraclonidine		- is used in open angle glaucoma as eye drops. (acts by decreasing aqueous humor formation)	-	
	Reserpine	-interferse with NA storage.	-		
Adrenergic Receptor Blockers	**Phenoxybenzamine**	-irreversible block of both α2&α1 receptors (long action-24h)	-pheochromocytoma (before surgical removal)	-postural hypotension -tachycardia -nasal stuffiness of congestion -vertigo&drowsiness -male sexual dysfunction (inhibits ejaculation)	-patients with decreased coronary perfusion. -can precipitate arrhythmias and angina
	Phentolamine	-reversible blocking of α2&α1 receptors (short action 4h)			-
	Prazosin	-selective α1 antagonist (short half life)	-urinary obstruction of benign prostatic hypertrophy (BPH). -treatment of essential hypertension with prostate enlargement. -Raynaud's disease	-decrease arterial pressure -less reflex tachycardia -first dose may produce an **orthostatic hypotensive response** can result in syncope(fainting)	
	Doxazosin				
	Terazosin	-selective α1 antagonist (long half life)			
	Tamsulosin	-selective α1A antagonist (in prostate)	-benign prostatic hypertrophy (BPH)	as non selective but to a lesser degree	
	Yohimbine	-α2 selective antagonist	-used as aphrodisiac in the treatment of erectile dysfunction.	-	

#2. β-Adrenoceptors blockers:

MOA	β-adrenergic blockers
Contraindications	-heart block. -Bronchial asthma & emphysema (safer with β1-selective blockers) -Diabetic patients -peripheral vascular disease like Raynaud's disease (safer with β1-selective blockers) -Hypotension. -Alone in pheochromocytoma (**must** be given with an α-blockers)
Pharmacological Actions	-CVS: Negative inotropic, chronotropic, dromotropic effect, decrease CO. - Antiarrhythmic effects. -Antianginal effects. - Antihypertensive. -mask hypoglycemia in diabetic patients> coma. - Bronchoconstriction -blood vessel β2: increase peripheral resistance, decrease Blood flow to organ. - Intestinal motility. -Hypoglycemia, decrease lipolysis in adipocytes β3, Na retention secondary to decrease BP. - Reduce intraocular pressure.
Adverse effects	With nonselective b-blockers : Unwanted pharmacological actions. (C THE BALD FISH)

Classification of B-blockers

Drugs: (14)	Selectivity	Sympathomimetic Activity (ISA)	Membrane stabilizing effects	Lipid solubility	ADRs:
Sotalol	Non selective β-Antagonists	without ISA	—	Hydrophilic	**C THE BALD FISH** 1.Cold extremities 2.coronary spasm 3.high triglycerides 4.hypotension 5.heart failure 6.hypoglycemia 7.hallucinations 8.erectile dysfunction 9.bradycardia 10.bronchoconstriction 11.arrhythmia 12. Lack of energy 13.depression 14.fatigue 15. Intermittent Claudication 16. Sweating
Timolol		without ISA		Lipophilic	
		—		—	
Oxprenolol		with ISA		—	
Propranolol		without ISA	Present	Lipophilic	
Pindolol		with ISA		—	
Acebutolol	Selective β-1	with ISA	—	—	
Atenolol		without ISA		Hydrophilic	
Bisoprolol		without ISA		Hydrophilic	
Betaxolol		—		—	
Celiprolol		with ISA		—	
Esmolol		—		Hydrophilic	
Metoprolol		without ISA		Lipophilic	
Carvedilol	Mixed nonselective β-α	without ISA		Lipophilic	-orthostatic hypertension -edema
Labetalol		with ISA	Present	Lipophilic	-orthostatic hypotension -sedation/dizziness

#2. β-Adrenoceptors blockers:

Drug	Pharmacodynamic Classification	Pharmacokinetic Classification	Uses
Propranolol	- Non-selective blocks β1&β2. -No intrinsic sympathomimetic activity (ISA). -has membrane stabilizing effects	-Lipophilic	-hypertension -anxiety (especially social & performance type) -migraine(prophylaxis) -cardiac arrhythmia -myocardial infarction -hyperthyroidism (thyrotoxicosis)
Timolol	-Non-selectiveβ1&β2 -without ISA.	-Lipophilic	-chronic glaucoma as eye drops
Atenolol	-Selective β1-antagonist -without ISA.	-	-hypertension -cardiac arrhythmia -myocardial infarction
Bisoprolol		-	-hypertension -cardiac arrhythmia (preferred) -hyperthyroidism -congestive heart failure
Metoprolol		-Lipophilic	-hypertension -myocardial infarction -congestive heart failure
Esmolol	-Selective β1-antagonist	-half life;10min (Ultra short action) -I.V	-cardiac arrhythmia
Carvedilol	-Non-selective blocks α&β -No ISA & local anesthetic effect. -Has antioxidant action.	Lipophilic	-used effectively in congestive heart failure -cardiac arrhythmia (preferred) -hypertensive emergency
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

#3. Anti-Arrhythmic drugs

Class I "Quarter Pounder with Lettuce Mayo and Fries" Na+ channel blocker (membrane stabilizing drugs)

Subclass: IA "Quarter Pounder" (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** -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 "with Lettuce,Mayo" (Shorten action potential duration)

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

Subclass: IC "and Fries" (No effect on action potential duration)

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.		**Proarrhythmia** 2- CNS : dizziness , tremor, blurred vision, abnormal taste sensations, paraesthesia. 3- Heart failure due to -ve inotropic effect

#3. Anti-Arrhythmic drugs

Class II
β-Adrenoreceptor blocker

Drug	**Esmolol**	**Propranolol , Atenolol, metoprolol**
Mechanism of action	block β1 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	
Clinical uses	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)	Used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias

Class III
K+ channel blocker

Drug	**Amiodarone**		
Pharmacological 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)** 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	**(pharmacokinetic)** Drugs (or substances) that inhibit CYP3A4 & CYP2C8 enzymes cause increase in serum concentration of amiodarone e.g Loratadine, Ritonavir Trazodone, Cimetidine, Grapefruit juice	**(pharmacokinetic)** Drugs that induce these enzymes Cause decrease in serum concentration of amiodarone e.g. Rifampin

#3. Anti-Arrhythmic drugs

Class III
K+ channel blocker

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

Class IV
Ca++ channel blocker

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

Class V
Miscellaneous Antiarrhythmic Drug

Drug	**Adenosine**
MOA	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**)
Clinical Use	Drug of choice for acute management of paroxysmal supraventricular tachycardia preferred over verapamil (because it's safer and does not depress contractility)
ADR's	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)**
Pharmacokinetics	**Half-life is less than 10 sec**

#3. Anti-Arrhythmic drugs

New Antiarrhythmic Drugs

Dronedarone

Overview	Pharmacological Action	Clinical uses	Contraindications
A non-iodinated congener of Amiodarone	It has antiarrhythmic properties belonging to all four classes	maintenance of sinus rhythm following cardioversion in patients with atrial fibrillation	-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)

Bradyarrhythmias

Atropine

Clinical uses

-Used in sinus bradycardia after myocardial infarction and in heart block
-In emergency heart block isoprenaline may be combined with atropine (caution)

Nonpharmacologic Therapy of Arrhythmias

Implantable Cardiac Defibrillator (ICD):

- Can automatically detect and treat fatal arrhythmias. such as ventricular fibrillation.
- used if pharmacological options didn't work(Note)

#4. Drug therapy for heart failure:

Drug that decrease Preload

class	drug	MAO	Use
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
	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 Isosorbide Dinitrate	↑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 and edema

Drug that decrease Afterload

Drug	class	MAO
Arteriodilators: Hydralazine	reduce peripheral vascular resistance.	when the main symptom is rapid fatigue due to low cardiac output.

Drugs that decrease both preload & afterload

class	drug	MAO	P.K	Use	class
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 =Decrease mortality rate	-Rapidly absorbed from GIT after oral administration - Food reduce their bioavailability. ——————— Ramipril & Enalapril: -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 hypertension	-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 vasodilator	Sodium nitroprusside	by ↑ cGMP	-Acts immediately -effects lasts for 1-5 min.	- Given I.V In acute or severe heart failure	-

#4. Drug therapy for heart failure:

Drugs that increase contractility

class	drug	MAO	Use	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 (Rhythm) Extrasystoles Ventricular tachycardia & fibrillation Cardiac arrest Noncardiac ADRS: 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. 1.in cardiomyocytes⟶ Increases cardiac contractility. 2.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

class	drug	MAO	Use
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

Congestive heart failure in black patients

Hydralazine (Arterial Dilator)/ **isosorbide dinitrate** (venodilators) **fixed dose combination.**

- **FDA** approved to add to standard therapy for black Americans with Congestive heart failure (due to poor response to ACE inhibitors).
- Should be considered for patient intolerant to ACE inhibitor & ARBs due to renal dysfunction.

#5. Anti-hypertensive drugs:

1.Diuretics

Class	Thiazides	Loop Diuretics	Potassium-sparing Diuretics
Drugs	chlorthalidone Hydrochlorothiazide	Furosemide	
Action	The initial diuresis lasts 4-6 weeks and then replaced by a decrease in the PVR (Peripheral vascular resistance	-More potent diuresis but a smaller decrease in PVR -Hypertension with **renal impairment** or **heart failure** (edema)	Minimal effect on BP
Uses	Mild to moderate Hypertension		

2.Drugs acting on the renin angiotensin aldosterone (RAAS) system:

a. Angiotensin Converting enzyme inhibitors (ACEIs)

Drugs	Captopril, Lisinopril, Enalapril, Ramipril
P.K	-Polar→Do not cross BBB -Long half life & given once daily -Excreted in urine -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**, Enalaprilat is the active metabolite of Enalapril, can be given by I.V. route in hypertensive emergency.
M.O.A	-Particularly effective when hypertension results from **excess renin** production (renovascular hypertension, white & young) -Their effect result primarily from vasodilation (reduction of peripheral resistance) with little change in cardiac output -A fall in aldosterone production may also contribute.
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 of nose, tongue, throat & larynx)→caused by inhibition of bradykinin that accumulate in bronchial mucosa. -First dose effect **ADRs effects Specific to captopril**: skin rash, fever, dysgeusia ,Proteinuria, and neutropenia.
Contraindications	-The second and third trimesters of **Pregnancy** due to the risk of: fetal hypotension, anuria, renal failure & malformations. -Renal artery stenosis. -Potassium-sparing diuretics. -NSAIDs . (Impair their hypotensive effects

#5. Anti-hypertensive drugs:

2.Drugs acting on the renin angiotensin aldosterone (RAAS) system continued:

b. Angiotensin receptors blockers (ARBs)

Drugs	Losartan	Valsartan
P.K	-Has a Potent active metabolite. -**Orally** effective -Taken once daily. -long half life. -Do not cross BBB.	No active metabolite
M.O.A	-Selective block of **AT1** receptors. -Produce more complete inhibition of angiotensin than ACE inhibitors -why?because there are other enzymes (not only ACE) that can generate angiotensin -No effect on bradykinin	
ADRs	Same as ACEI **except** :No effect on bradykinin, no cough, no angioedema.	
contraindication	Same contraindications as ACEI .	

3. Calcium channel blockers (**V**ery **N**Ice **D**rugs)

Class	Phenylalkylamine	Dihydropyridine	Benzothiazepine
Drugs	**V**erapamil	**N**ifedipine	**D**iltiazem
Action	Act mainly on **myocardium**	Dihydropyridine group act mainly on **smooth muscle**	Has intermediate effect
P.K	-Have active metabolite -Highly bound to plasma proteins (more than 90%)	-Doesn't have active metabolite -Highly bound to plasma proteins (more than 90%)	-Have active metabolite -Less Bound to plasma proteins(70-80%).
	-Given orally or I.V. injection : (onset 1-3min after IV , 0.5-2hr after oral) -Well absorbed -Sustained-release preparations can permit once-daily dosing.		
M.O.A	Block the influx of calcium through calcium channels resulting in: 1- Peripheral vasodilatation. 2- Decrease cardiac contractility		
Uses	**-Treatment of chronic hypertension.** -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		

#5. Anti-hypertensive drugs:

4. Vasodilators

Classified into arterial , venous , mixed vasodilators

Drug	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Site of action	Arteriodilators			**Artiodilator & venodilator**
Action	Once administered, fall in BP produced, will activate the sympathetic system & the RAAS.			
M.O.A	Release of nitric oxide (NO)	Opening of **potassium** channels in smooth muscle membranes by minoxidil sulfate (Active metabolite)	Opening of potassium channels	Release of nitric oxide (NO)
Administration	Oral		Rapid I.V	I.V infusion
Therapeutic Uses	Moderate-severe hypertension		Hypertensive emergency	
Uses In combination with diuretics & β-blockers	Hypertensive pregnant woman	Baldness	Treatment of 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 excess hair growth **Contradicted 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 → **cyanide poisoning** (metabolic acidosis, arrhythmias, severe hypotension and death)

#5. Anti-hypertensive drugs:

5. Sympatholytic drugs

a. Centrally acting sympatholytic drugs

Drug	Clonidine	α-methyldopa
M.O.A	-α2 agonist -diminishes central adrenergic outflow -↑parasympathetic outflow to the heart.	-α2 agonist -Converted to methyl noradrenaline centrally to diminish the adrenergic outflow from the CNS -Lead to a reduced total peripheral resistance and a decrease BP.
Uses	-Hypertension complicated with **renal disease** ⟶ it does not decrease renal blood flow or glomerular filtration -Resistant Hypertension	The first line treatment of hypertension in **pregnancy**
ADRs	Abrupt withdrawal of can lead to **rebound hypertension.**	-

b. α-adrenoceptor blockers

Drug	Prazosin	Doxazosin
P.K	Short-acting	Preferred cause of its half life
M.O.A	-Blocks α1 receptors in arterioles and venules -Reduce blood pressure by decreasing preload and afterload	

c. B-adrenoceptor blockers

Drug	Propranolol	Atenolol	Metoprolol
Type	Non-selective	Selective beta 1 blocker	
M.O.A	They **lower blood pressure** by: -Decrease cardiac output - Inhibiting the release of renin release - Central mechanism		
Uses	-Should not be the primary agent for primary prevention but are effective as **add-on therapy.** -May take two weeks for optimal therapeutic response -In patient with concomitant coronary heart disease -When discontinued should be withdrawn gradually		
ADRs	-Hypoglycemia -Fatigue -Mask the symptoms of hypoglycemia in diabetics -Erectile dysfunction -Increased triglycerides -Aggravate peripheral arterial disease		

#6. Anti-Anginal drugs:

Traditional Approaches [NBC]

1) Organic Nitrates [NBC]

Drug	Short-acting **Nitroglycerin**	Long-acting **Isosorbide Mononitrate**
M.O.A.	Supply of **NO** by nitrates → activation of **guanylate cyclase** in vascular smooth muscle → ↑ **cGMP** → activation of **protein kinase G** → smooth muscle relaxation → vasodilation	
Hemodynamic Effects	1) Venous dilation → ↓ **preload** 2) Coronary dilation → ↑ **myocardial perfusion** 3) Arterial dilation → ↓ **afterload** 4) **Shunting** of flow from normal area to ischemia area by **dilating** collateral vessels	

Indications	**Sublingual**
	▪ **Stable angina**
	  ▪ Situational prophylaxis
	  ▪ Acute symptom relief
	▪ **Variant angina**
		IV
		▪ **Unstable angina**
		▪ **Acute MI**
		▪ **Refractory AHF**
			▪ **Stable angina**
			  ▪ Persistent prophylaxis
			▪ **Congestive HF** (with **Hydralazine**)
			  ▪ When **ACEIs** are contraindicated

Contra-indications	1) **Sensitivity** to organic nitrates 2) **Glaucoma** 3) **Uncorrected hypovolemia** 4) ↑ **Intracranial pressure** (e.g. head trauma or cerebral hemorrhage) 5) **PDE_5 inhibitors** (e.g. Sildenafil) with **nitrates** → severe hypotension → death	
ADRs	▪ **Throbbing headache** ▪ **Flushing** ▪ **Postural hypotension (dizziness)** → reflex **tachycardia (palpitations)** → **syncope** ▪ Rarely: **methemoglobinemia** ▪ **Nitrate tolerance:** loss of vasodilator response of nitrates on long-term use	

2) β_1-Selective Blockers [NBC]

Drug	**Atenolol | Bisoprolol | Metoprolol**	
M.O.A.	▪ ↓ **HR** & **contractility** → ↑ duration of **diastole** → ↑ **coronary blood flow** → ↑ O_2 supply → ↓ **workload** → ↓ O_2 consumption	
Indications	**Angina**	Stable	Regular prophylaxis → 1st line for chronic use (may be combined with nitrates)
		Unstable	Stop progression to MI & improve survival
		Variant	Contraindicated
	MI		↓ Infarct size + ↓ morbidity & mortality + ↓ O_2 demand + ↓ arrhythmias

3) Calcium Channel Blockers (CCBs) [NBC]

Group	**Dihydropyridines**	**Non-dihydropyridines**	
		Phenylalkylamine	**Benzothiazepine**
Drug	**Nifedipine | Nicardipine | Amlodipine**	**Verapamil**	**Diltiazem**
Selectivity	Vascular smooth muscle	Cardiomyocytes	Intermediate (both)
M.O.A.	**Block L-type Ca^{2+} channels** → ↓ frequency of Ca^{2+} channel opening in response to depolarization → ↓ entry & release of Ca^{2+} → no stimulus contraction-coupling → relaxation		
Indications	**Angina**	Stable	Regular prophylaxis (2nd line; if β-blockers are contraindicated or angina persists)
		Unstable	Rarely added if refractory to 1st line
		Variant	Attacks prevented; sometimes variably aborted

#6. Anti-Anginal drugs:

New Approaches

1) Metabolically Acting Agents

Drug	**Trimetazidine**
M.O.A.	**Blocks β-oxidation of free fatty acids** → ↑ use of glucose as an energy source (note: glucose requires less O_2 than fatty acids) → ↓ **O_2 demand** without altering hemodynamics
Indications	**Add-on** therapy
Contra-indications	▪ **Hypersensitivity** reaction ▪ **Pregnancy** & **lactation**
ADRs	**GIT disturbances**

2) Potassium Channel Openers

Drug	**Nicorandil**	
M.O.A.	**Dual mechanism**	
	1) **K_{ATP} channel opener:** ▪ Vascular smooth muscle: hyperpolarization → **vasodilation** ▪ Cardiomyocytes: repolarization → ↓ **cardiac work**	2) **NO donor:** ↑ cGMP & protein kinase G → vasodilation
Indications	**Prophylactic 2nd line** therapy in **stable** angina + **refractory variant** angina	
ADRs	▪ Flushing, headache, hypotension, palpitation, weakness (due to nitric oxide) ▪ Mouth & peri-anal ulcers (special to Nicorandil), nausea & vomiting	

3) Sinus Node Inhibition

Drug	**Ivabradine**
M.O.A.	**Blocks funny current (I_f)** that activates pacemaker cells of SA node
Effect	↓ slope of depolarization, ↓ HR, ↓ myocardial work, ↓ O_2 demand
Indications	▪ **Chronic stable angina** in patients with normal sinus rhythm but cannot take **β-blockers** ▪ **Heart failure** in patients inadequately controlled by **β-blockers** alone → **combined therapy**
ADRs	**Luminous** phenomena

4) Late Na^+ Current Inhibition

Drug	**Ranolazine**
M.O.A.	**Inhibits** the **late sodium current** (which increases during ischemia)
Indications	**Chronic angina** in **combination** with other drugs
Contra-indications	▪ **Prolongs QT interval** → contraindicated with **Class Ia** (Quidine & Procainamide) & **Class III** (Ibutilide) antiarrhythmics ▪ **Toxicity** due to interaction with CYP450 inhibitors (e.g. Diltiazem, Verapamil, Ketoconazole, Macrolides, grapefruit juice)
ADRs	**Dizziness** & **constipation**

#7.Thrombolytic drugs:

Non-fibrin specific plasminogen activators "USA"

Activate both plasminogen bound to clot surface and circulating plasminogen in blood leading to extensive systemic plasminogen activation, with degradation of several plasma proteins including fibrinogen, factor V, and factor VIII.

	Streptokinase	Anistreplase	Urokinase
M.O.A	Is a **bacterial protein** produced by B-hemolytic streptococci. It acts **indirectly** by forming plasminogen- streptokinase complex **"activator complex"** which converts inactive plasminogen into active plasmin. -Can degrade fibrin clots as well as fibrinogen and other plasma proteins.	**(APSAC)** **Anisoylated Plasminogen Streptokinase Activator Complex** acylated plasminogen combined with streptokinase. It is a **prodrug**—> de-acylated in circulation into the active plasminogen-streptokinase complex. (to reduce systemic plasminogen activation ^bleeding^)	**Human enzyme** synthesized by the kidney obtained from either urine or cultures of human embryonic kidney cells. **is a direct plasminogen activator.**
T1\2	less than 20 minutes.	70-120 min	12-20 minutes
Administration	intravenous infusion	bolus I.V. injection	intravenous infusion
Advantages	It is the **least expensive** among others. used for **venous** or **arterial** thrombosis.	**Longer** duration of action than streptokinase. **More** thrombolytic activity. **Greater** clot selectivity.	**No anaphylaxis (not antigenic)** Used for the lyses of acute massive **pulmonary** emboli
Disadvantages And side effect	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).	Similar but less than streptokinase alone in: 1. Antigenicity. 2. Allergic reactions. 3. Minimal fibrin specificity Systemic lysis. **4. But more expensive than streptokinase**	1. Minimal fibrin specificity 2. Systemic lysis (acts upon fibrin-bound and circulating plasminogen). 3. **Expensive** (its use is now limited).
Precautions	**Not used in patients with:** **1-Recent streptococcal infections** **2-Previous administration of the drug** These patients may develop fever, allergic reactions and resistance upon treatment with streptokinase due to antistreptococcal antibodies.	-	-

#7.Thrombolytic drugs:

Fibrin specific plasminogen activators "ART"

Fibrin specific plasminogen activators activate mainly plasminogen bound to clot surface and have less effect on circulating plasminogen.

Recombinant human tissue plasminogen activators (t–PA)

	Alteplase	**Reteplase**	**Tenecteplase**
M.O.A	- Prepared by recombinant DNA technology. -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.**		
T1\2 (ART from low to high)	very short (~5min)	Longer (15 min.)	more than 30 min (longest)
Administration	intravenous bolus followed by an infusion.	**two** I.V. bolus injections	**single** IV bolus.
Advantages	-Fibrin-specific drugs (clot specific). -Limited systemic fibrinolysis. -Reduced risk of bleeding -Not-antigenic **(can be used in patients with recent streptococcal infections or antistreptococcal antibodies**).		
Degree of specificity	-	enhanced fibrin specificity	more fibrin-specific than alteplase.
uses	-ST-elevation myocardial infarction (STEMI) -Pulmonary embolism.		It is only approved for use in acute myocardial infarction.
Contraindications to thrombolytics (for both specific and non-specific	**Absolute contraindications** include: -Active internal bleeding -Cerebral hemorrhagic stroke -Recent intracranial trauma or neoplasm -Major surgery within two weeks **Relative contraindications** include: -Active peptic ulcer -Severe uncontrolled hypertension		

Fibrinolytic inhibitors (Antiplasmins) inhibit plasminogen activation and thus inhibit fibrinolysis and promote clot stabilization.

drug	**Aminocaproic Acid & tranexamic acid**	**Aprotinin**
M.O.A	competitive inhibition of plasminogen activation	inhibits fibrinolysis by blocking the action of plasmin (plasmin antagonist)
Administration	orally	orally or i.v.
Uses	-Adjuvant therapy in hemophilia -Fibrinolytic therapy-induced bleeding (antidote). -Post-surgical bleeding -These drugs work like antidotes for fibrinolytic drugs.Similar to Protamine (Antidote of the anticoagulant, heparin) or Vitamin K (Antidote of the oral anticoagulant warfarin). Dr: additional information	

#8.Hyperlipidemia

Targets Exogenous cholesterol

Bile acid sequestrants/ Resins

	Cholestyramine	Colestipol	Colesevelam
MOA	1.Bind to bile acids in the small intestine & form insoluble complex that cannot be reabsorbed 2. Decreased LDL to liver 3.In liver :increased LDL receptors —>more cholesterol (to convert it to bile salts)—> reduced levels of serum LDL **(no effect on HDL levels)**		
USES	**second** line therapy for hypercholesterolemia		
CONTRA	Biliary obstruction, chronic constipation & ,hypertriglyceridemia(**TG** >400 mg/dL).		
ADRs	-GIT upset: abdominal discomfort, bloating, constipation. - Decreased absorption of fat soluble vitamins (A, D, K).		
DRUG interactions	Interfere with the absorption of many drugs ex. (Statins, ezetimibe, chlorothiazides ,digoxin, &warfarin) **Therefore, other drugs should be taken 1 hour before, or 4 hours after taking resins.** Except **colesevelam**, it doesn't interfere with the absorption of other drugs		

Cholesterol Absorption Inhibitors (Ezetimibe)

MOA	Inhibits intestinal cholesterol absorption by inhibiting(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(**↑4%**) and triglycerides(**↓8%**)**
USES	Hypercholesterolemia. Usually used in conjunction with a statin (synergistic effect).
ADRs	Not common But may occur: GIT disturbance, headache, fatigue, arthralgia and myalgia

Targets Endogenous cholesterol

Fibrates (fibric acid derivatives)

	Clofibrate	Gemfibrozil	Fenofibrate
MOA	• Peroxisome proliferator activated receptor agonists (PPARα) . • These receptors Increase transcription ol LPL → ↑ catabolism of TG in VLDL & chylomicrons They cause : 1. ↑ LPL activity , ↑ clearance of VLDL & chylomicrons 2. A marked reduction in TG (due to catabolism of VLDL). 3. ↑FFA uptake by the liver 4. ↑LDL-C uptake by the liver. 5. ↑ HDL-C by ↑ it's apoprotein production 6. ↑ 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		
USES	1st-line defense for: • Mixed dyslipidemia (i.e. raised serum TG and C). • Low HDL levels & ↑ risk of atheromatous disease (often type 2 DM) • Severe treatment-resistant dyslipidemia		
CONTRA	-Severe hepatic or renal dysfunction. -Pregnant or nursing women - preexisting gallbladder disease		
ADRs	GI distress, rash, myopathy, gallstones.		
Drug interactions	Increased risk of myopathies when used with statins Displace drugs from plasma proteins → Potentiates effects of oral anticoagulant like warfarin & oral hypoglycemics		

#8.Hyperlipidemia

Targets Endogenous cholesterol

Statins

	Atorvastatin	fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
MOA	HMG-CoA reductase inhibitor. (rate limiting step) 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.					
USES	1. **First-line therapy** to reduce hyperlipidemia & type 2a hyperlipoproteinemia 2. Used In diabetics and patients with insulin resistance (**combination therapy)** 3. Mixed dyslipidemias (**combination therapy** with fibrates & niacins) 4. 2ry prevention in all ischemic insults (stroke or MI..)					
CONTRA	-Pregnancy -Liver disease					
ADRs	- Common side effects: Headache, myalgia ,fatigue, GI intolerance and flu-like symptoms **Hepatotoxicity ↑concentration of serum aminotransferases.** **Myopathy ↑[CK]** **Teratogenicity**					
DRUG INTERACTIONS	Oral anticoagulants & antidiabetic drugs (displacement from plasma protein binding sites) Fibrates (↑ risk of myopathy). Drugs metabolized by 3A4 isoform of cytochrome P450 like: erythromycin, verapamil ,cyclosporine, ketoconazole. **Except pravastatin & fluvastatin** , safe in patients taking other drugs metabolized by CYP3A4 system					
PK	Metabolized by CYP3A4. Taken at bedtime because hepatic C synthesis is maximal between midnight & 2:00 am. **Except atorvastatin** taken at any time because of its long T½ (14 hrs).					

Targets Endogenous cholesterol

Niacin (nicotinic acid)

MOA	Water soluble B-complex vitamin with multiple actions 1. Adipose tissue:Inhibits nicotinic acid receptors → ↓fatty acid mobilization to the liver → ↓TG & thus VLDL hepatic synthesis 2. In liver: inhibits 2-diacylglycerol acyltransferase , key enzyme for TG synthesis. 3. In Plasma: ↑ peripheral lipoprotein lipase activity → improved VLDL clearance and chylomicrons
Phama. Actions	1. Reduction of hepatic VLDL synthesis why? - ↓ synthesis in liver , ↑ clearance in plasma , ↓ mobilization of FA from adipose. 2. ↓ LDL : due to the reduction of it's precursor VLDL 3. Remarkable increase in HDL : (unknown mechanism) , also promotes hepatic apoA-I production & slows hepatic clearance of apoA-I & HDL → ↓ HDL catabolism.
USES	Type IIa hypercholesterolemia, Type IIa & IIb hypercholesterolemia with any combines hyperlipidemia Mixed dyslipidemias Hypertriglyceridemia with low HDL-C levels
CONTRA	Gout - Peptic ulcer - Hepatotoxicity - Diabetes mellitus
ADRs	MOST COMMON: Flushing (prostaglandin mediated) → avoided by low dose Aspirin ½ hour before niacin GI distress: dyspepsia, nausea,vomiting, reactivation of peptic ulcer (can be↓ if taken after meal) High doses: hepatotoxicity (reversible ↑ in liver enzymes) Impairment of glucose tolerance → overt diabetes ↑ uric acid → gout.

Good luck!

Pharmacology
TEAM 441

Team leaders

Alanoud Alhaider

Faisal Alhussaini

Subleader

Leen Alhadlaq

A big thanks to our amazing team members !

Ghadah Fahad
Sarah Alotaibi
Norah Alqazlan
Nourah Alkhudiri
Arwa Almobeirek
Reema Alrashedi

MED441
KING SAUD UNIVERSITY

Contact us:
Pharmateam441@gmail.com