PHARMACOLOGY

Lecture: Heart failure 5,6

OBJECTIVES:

By the end of this lecture, students should be able to:

- **Describe** the different classes of drugs used for treatment of acute & chronic heart failure and their mechanism of action.
- **Understand** their pharmacological effects, clinical uses, adverse effects and their interactions with other drugs.

PHARMACOLOGY
435

- Important.
- Extra notes.
- Mnemonic.

Heart failure

Heart failure

The inability of the heart to maintain an adequate cardiac output to meet the metabolic demands of the body.

Factors affecting cardiac output and heart failure:

- Cardiac contractility (↓ in HF)
- Afterload (↑ in HF)
- Preload (↑ in HF)

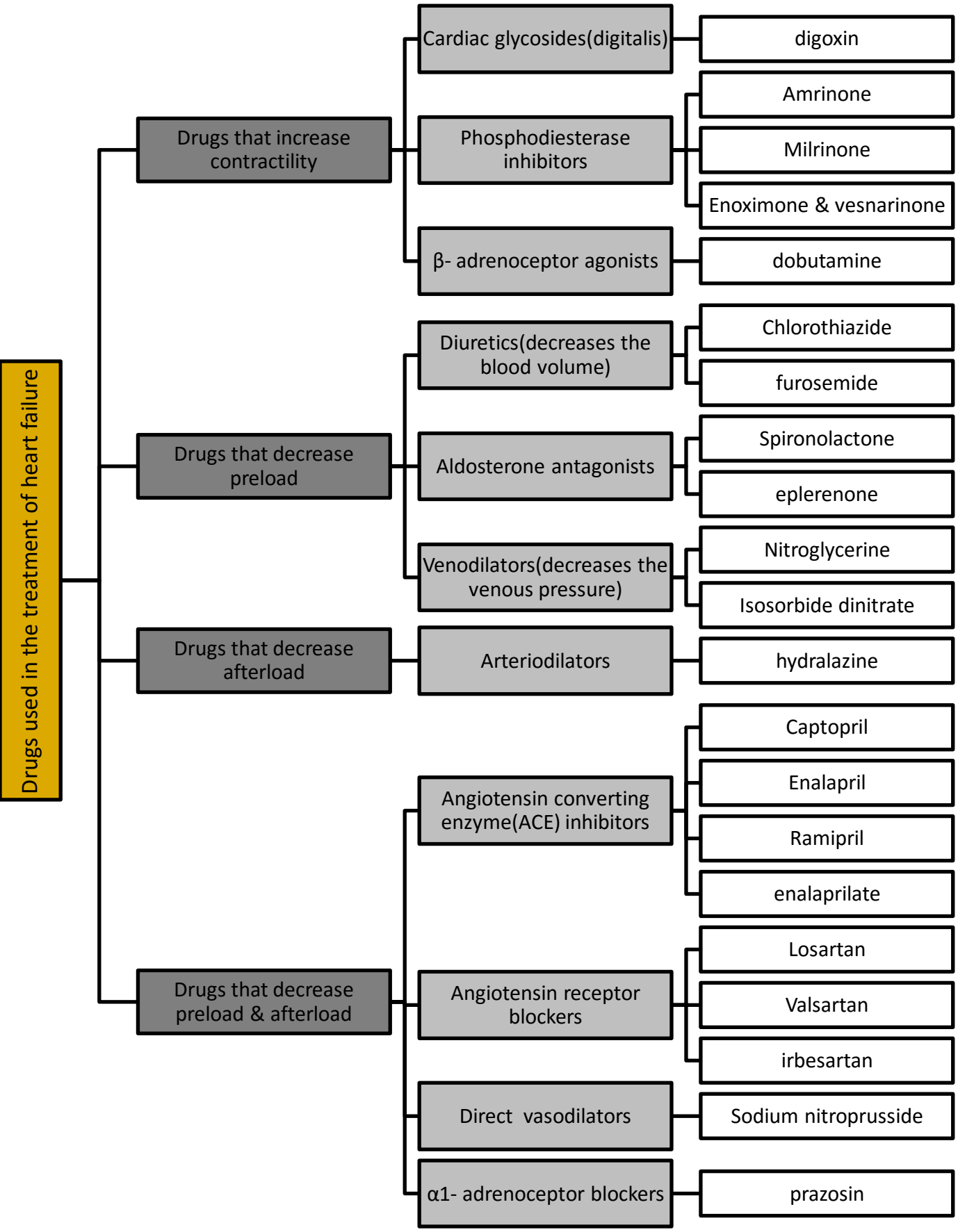
Causes

- High blood pressure.
- Abnormal heart rhythm
- Cardiomyopathy
- Disorder of coronary arteries.
- Heart valve disorders

Symptoms

- Tachycardia(due to reflex sympathetic discharge)
- Decreased exercise tolerance (rapid fatigue).
- Dyspnea(pulmonary congestion).
- Peripheral edema(feet in particular)
- Cardiomegaly (dilation in the heart) after some time of having heart failure

Drugs used in the treatment of heart failure



I. Drugs that decrease preload

Group	Diuretics		Aldosterone antagonists		Venodilators
Mechanism of action	↓ salt & water retention → ↓ ventricular preload / venous pressure → ↓ cardiac size → improve cardiac performance		Antagonizes the action of aldosterone at mineralocorticoid receptors		Dilate venous blood vessels & ↓ preload
Drugs	Chloro-thiazide	Furose-mide	Spirono-lactone	Eplere-none	Nitroglycerine Isosorbide dinitrate
Use	First-line agent in heart failure therapy used in mild congestive HF + pulmonary & perph. edema → side effect (hypokalemia so→ give K supplements)	Potent diuretic Used for immediate reduction of pulmonary congestion & severe edema associated with ▪ Acute HF ▪ Moderate & sever Chronic failure	- Nonselective antagonist of aldosterone receptor -A potassium sparing diuretic used in congestive heart failure - Improves survival in advanced heart failure	A new selective aldosterone receptor antagonists	I.V · used in severe HF when main symptom is Dyspnea due to pulmonary congestion -Use when ACE inhibitors are contradicted should be considered patients who are intolerant of an ACE inhibitors and an ARB due to renal dysfunction -In case of black patients with advanced HF due to left ventricular systolic dysfunction in addition to standard therapy.

II. Drugs that decrease afterload

Group	Arteriodilators
Mechanism	↓ peripheral vascular resistance
Drugs	Hydralazine
Use	▪ Used when the main symptom is Rapid fatigue due low cardiac output ▪ should be considered black patients with advanced heart failure due to left ventricular systolic dysfunction in addition to standard therapy. ▪ should be considered patients who are intolerant of an angiotensin converting enzyme inhibitor and an angiotensin II receptor blocker due to renal dysfunction

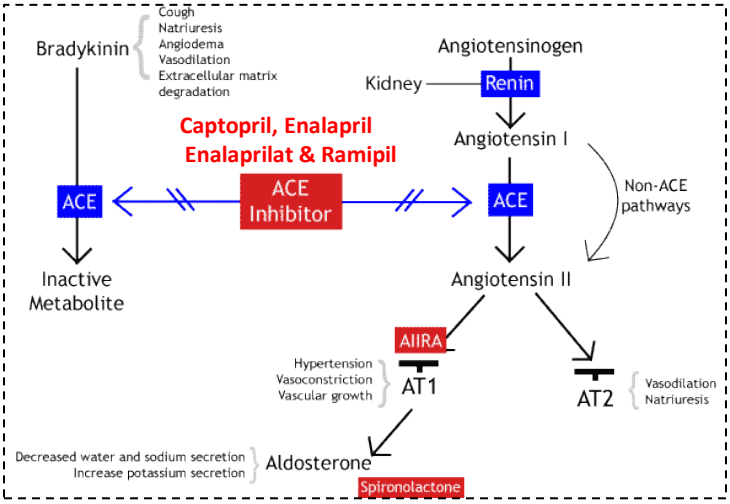
III. Drugs that decrease both preload & afterload

(Combined arteriolo- & venodilators)

Group	Angiotensin converting Enzyme (ACE) inhibitors			Angiotensin receptor blockers (ARBs)			α1-adrenocepters antagonists	Direct vasodilators
Mechanism of action	↓ ACE → reduce/inhibit synthesis of AgII → activation of Bradykinin system which is potent vasodilation → ↓ preload & afterload			Blocks AT1 receptors → block the action of AgII (more potent effectthan ACE)			Block α- receptors in arterioles and venules	Releasing Nitric oxide → vasodilation
Drugs	Captopril	Enalapril	Ramipil	Losartan	Valsartan	Irbesartan	Prazosin	Sodium Nitroprusside
Pharmacokinetics – Rout of administration	**Oral** Except the active metabolite of enalapril → Enalaprilat → Given I.V (in hypertensive emergency) **Note:** Enalapril & Ramipil are given as prodrugs (converted to their active metabolites in the liver), Captopril is NOT a prodrug			-			-	**I.V**
Pharmacokinetics – Absorption & Duration	▪ Rapidly absorbed from GIT after oral administration. ▪ Food reduce their bioavailability ▪ Enalapril & Ramipril have long half-life & given once daily							Acts immediately and effects lasts for 1-5 minutes
Effect	↓Peripheral resistance (Afterload) ↓Venous return (Preload) ↓sympathetic activity (By blocking sympathetic nerve release & reuptake of norepinephrine) ↓remodeling (cardiac & vascular) associated with chronic heart failure → ↓mortality rate						-	Potent vasodilating effects in arterioles and venules
Use	▪ Are now considered as first-line drugs for chronic heart failure along with diuretics ▪ First-line drugs for hypertension therapy			It's used with ACE drugs to decrease mortality rate			Reduce blood pressure by decreasing both afterload & preload which help heart failure patients	Used for acute or severe heart failure

Continued: ACE inhibitors

Recall: Mechanism of action:



ACE inhibitors Adverse effects & contradictions:

Mnemonic:
Captopril

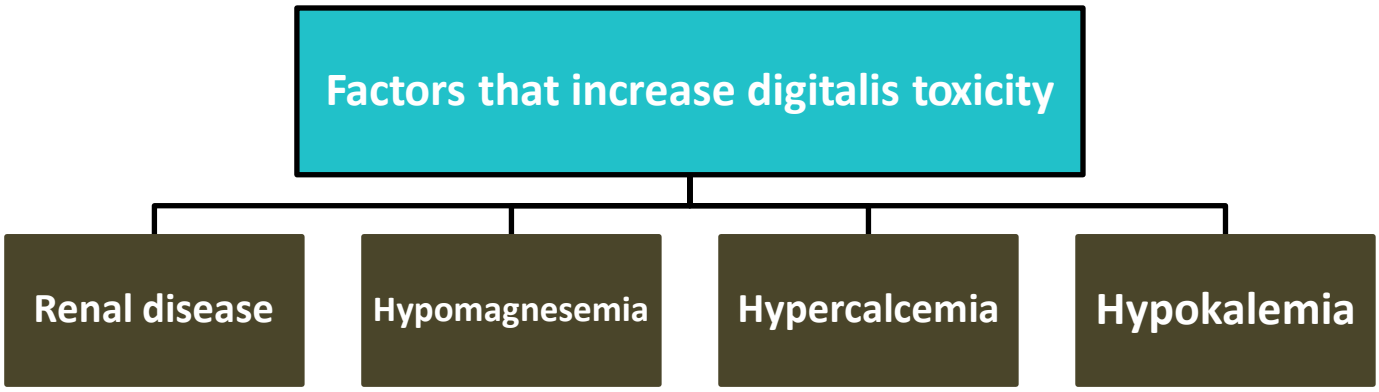
Group	ACE inhibitors
Adverse effects	1) **C**ough (dry) & sometimes with wheezing
	2) **A**ngioneurotic edema (swelling in the nose , throat, tongue, larynx)
	3) **P**otassium excess (hyperkalemia) especially in patients with renal insufficiency or diabetes
	4) **T**aste change (dysgeusia)
	5) **O**rthostatic hypotension → severe hypotension in hypovolemic patients (due to diuretics, salt restriction or gastrointestinal fluid loss)
	6) **P**regnancy (during the second and third trimesters) → contradiction (due to the risk of: ▪ Fetal hypotension ▪ Renal failure ▪ Malformations
	7) **R**enal failure → contradicted in renal artery stenosis
	8) **I**ncreased renin
	9) **L**iver toxicity

IV. Drugs that increase contractility

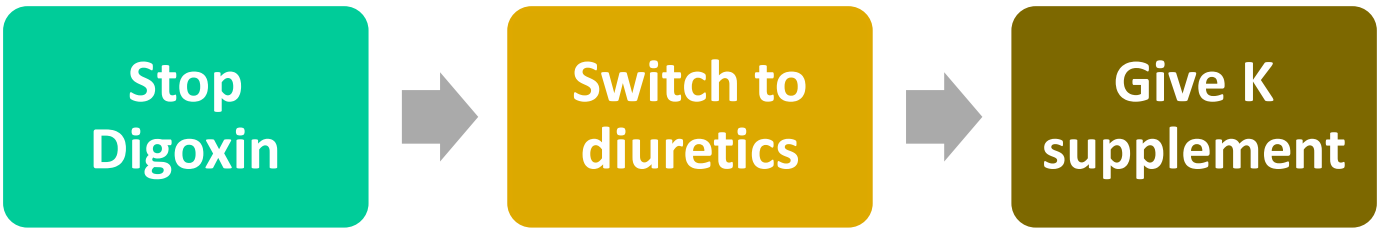
Group	Cardiac glycosides (Digitalis)	Phosphodiesterase -III inhibitors	β – Adrenocepters agonists
Effect	Increased contractility (+ve inotropic) *we give these drugs when there is problem in contractility		
Drugs	**Digoxin** Source: (from digitalis latana plant) *digoxin & digitoxin are the only inotropic drugs available that can be given orally.	Bipyridines: **Amrinone** / **Milirnone** New drugs in clinical trials: **Enoximone** / **vesnarinone**	**Dobutamine**
Mechanism of action	Inhibit Na/K ATPase enzyme (the sodium pump): 1-inhibit Na/K pump directly 2-indirect inhibition of Na/Ca exchange 3- facilitate Ca influx 4- ↑ Ca release from ER & T tubules *↑ extracellular K ↓ binding of cardiac glycosides to NA/K ATPase enzyme that explains ↑ toxicity in hypokalemia	Inhibit Phosphodiesterase isoenzyme III in (cardiac & blood vessels)→ inhibit cAMP degradation (↑cAMP) ↓ 1- in heart: ↑ Ca → ↑contraction 2- in peripheral vessels: dilatation → ↓ afterload & preload	Selective β1 agonist
Pharmacological action	1- ↑ force of myocardial contraction (+ve inotropic effect) → ↑left ventricle emptying →↑ Cardiac output *anything that ↑ efficiency of heart pump → ↓ dilated heart 2- ↓heart rate by vagal stimulation (↓ AV conduction)(-ve chronotropic effect)		+ve Inotropic effect
Use	1- Congestive heart failure 2- Atrial arrhythmias: ▪ Atrial flutter ▪ Atrial fibrillation ▪ Supraventricular tachycardia *digoxin protect heart from high rate	**Milirone:** Treatment of acute heart failure (I.V) not safe or effective in the longer treatment (> 48 hours)	Treatment of acute heart failure (Cardiogenic shock / I.V in severe cases)
Pharmacokinetics – Therapeutic index	Narrow		
Pharmacokinetics – Absorption	40%-80% Absorbed orally → variable bioavailability		
Pharmacokinetics – Excretion	85% Excreted unchanged in urine		

Adverse effects	Cardiogenic:	Non-cardiogenic:	Cardiogenic:	Non-cardiogenic:
	Digitalis – induced (arrhythmia): -Extrasystoles A.V.block -Coupled beats (Bigeminal rhythms) Normal SA impulse + coupled systole impulse -Ventricular tachycardia or fibrillation -Cardiac arrest.	-GIT : anorexia ,nausea, vomiting, diarrhea (early sign of toxicity) -CNS :headache, visual disturbances, drowsiness	Arrhythmias (less than digitalis)	-GIT upsets (Nausea ,vomiting) -Liver toxicity -Thrombocytopenia (Amrinone not used now because it causes thrombocytopenia)

Management of Digoxin adverse effects



Treatment of the adverse effects:



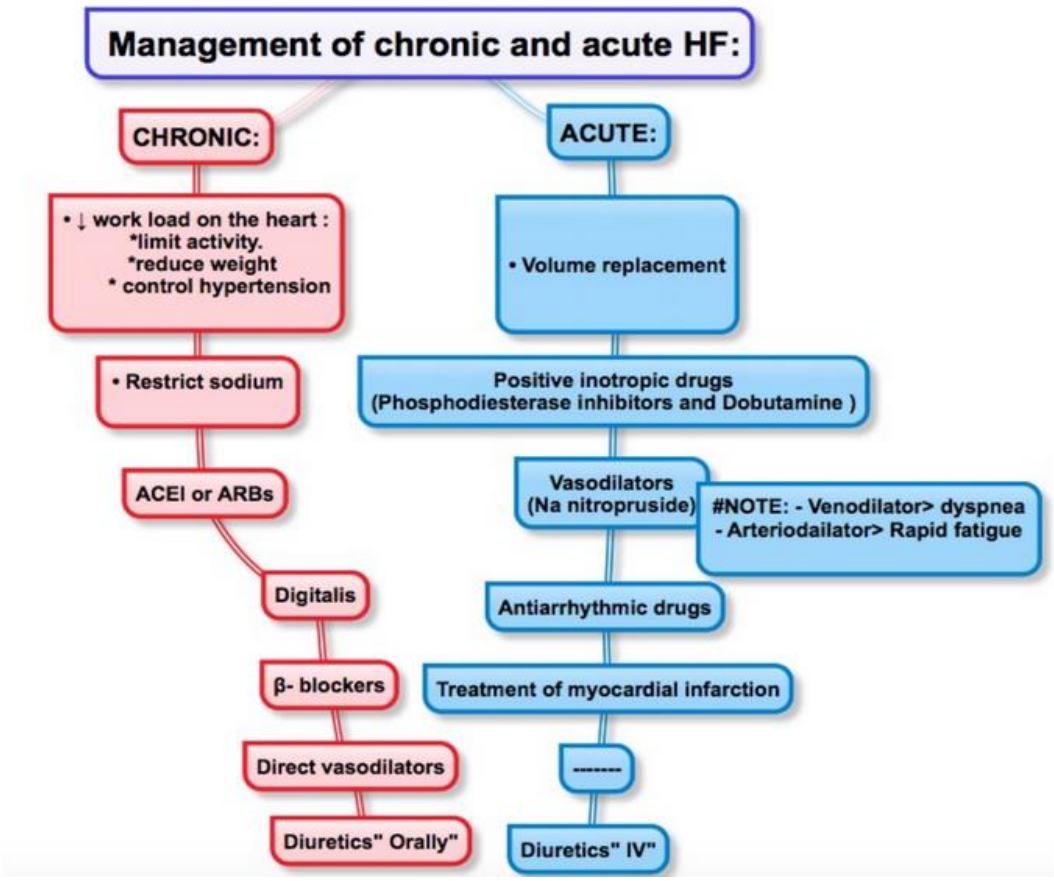
Other Heart failure drugs

Group	β-adrenoceptor blockers		B-type Natriuretic Peptides
Use	The elevated adrenergic activity in chronic heart failure patients cause structural remodeling of the heart (cardiac dilatation & hypertrophy) β-blockers: ▪ Reduce the progression of chronic heart failure ▪ Not used in acute heart failure		▪ BNP is secreted by the ventricular myocardium in response to stretch ▪ Elevated BNP is associated with advanced heart failure (compensatory mechanism in HF) ▪ Indicated for the treatment of patients with acutely decompensated heart failure who have dyspnea at rest or with minimal activity
Mechnism of action	1. attenuate cardiac remodeling 2. slow heart rate, which allows the left ventricle to fill more completely 3. decrease renin release ↓ reduce mortality & morbidity of patients with HF		Increases cyclic-GMP in vascular smooth muscle, leading to smooth muscle relaxation, & reduction of preload and afterload
Drugs	2nd Generation	3rd Generation	Nesiritide
	cardioselective (β_1-receptors) e.g. Bisoprolol, Metoprolol	Have vasodilator actions (α-blocking effect) e.g. Carvedilol , Nebivolol	Purified preparation of human BNP, manufactured by recombinant DNA technology

Classification & management of heart failure

New York Heart Association (NYHA) Functional Classification:

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina), slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m).Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.



QUIZ

THANK YOU FOR CHECKING OUR WORK

THE PHARMACOLOGY TEAM

Thanks to 434 pharmacology team

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435