PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

Drug Therapy of Heart Failure

Objectives:

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

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

helpful video

Editing file

What is Heart Failure?

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

Causes (acute or chronic):

- Heart valve disorder.
- High blood pressure.
- Cardiomyopathy.
- Abnormal heart rhythm.
- Disorder of coronary arteries
  e.g. atherosclerosis

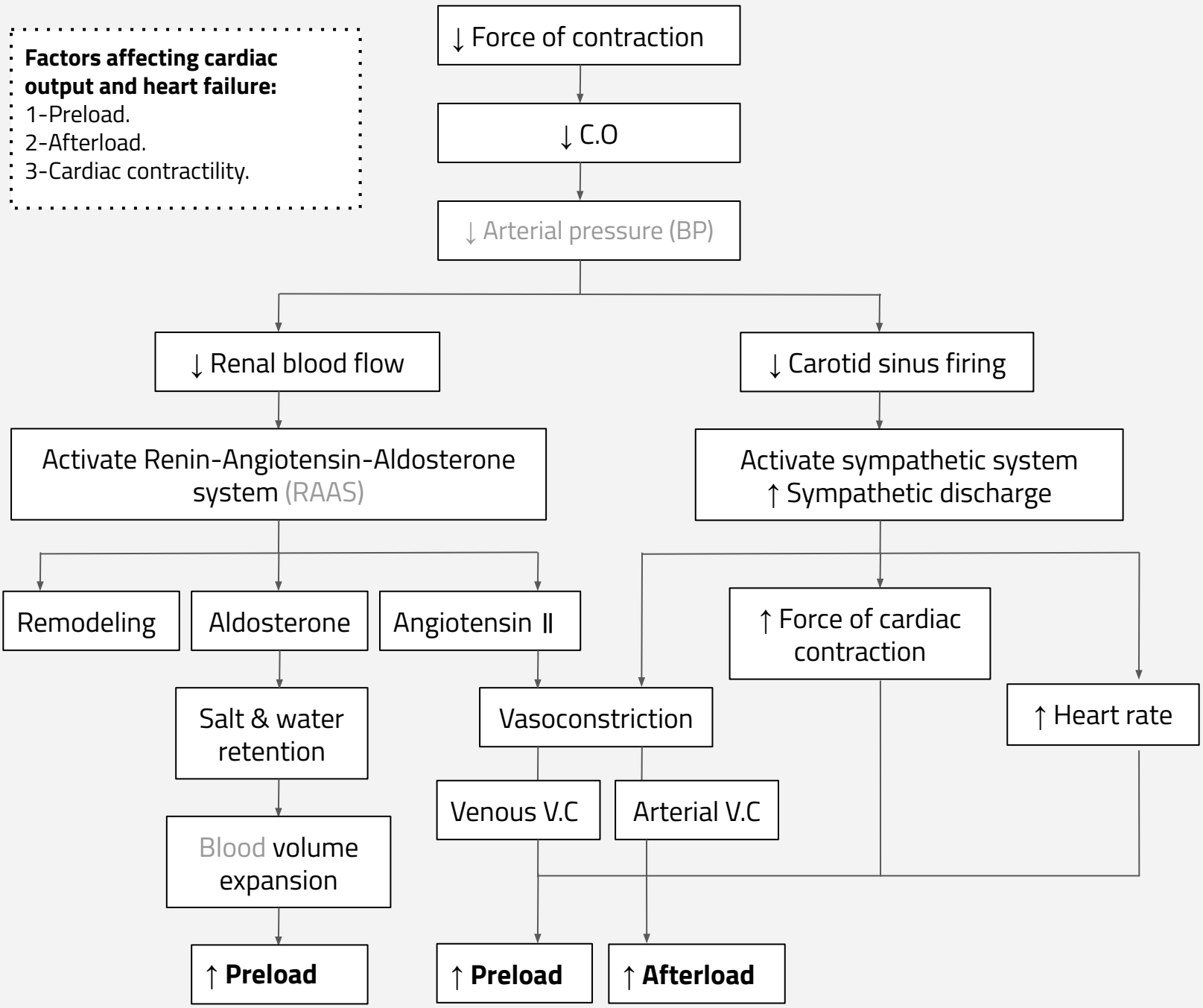
Symptoms:

- Tachycardia.
- Cardiomegaly. Abnormal enlargement of heart
- Decrease exercise tolerance (Rapid Fatigue).
- Peripheral edema.
- Dyspnea (Pulmonary congestion).

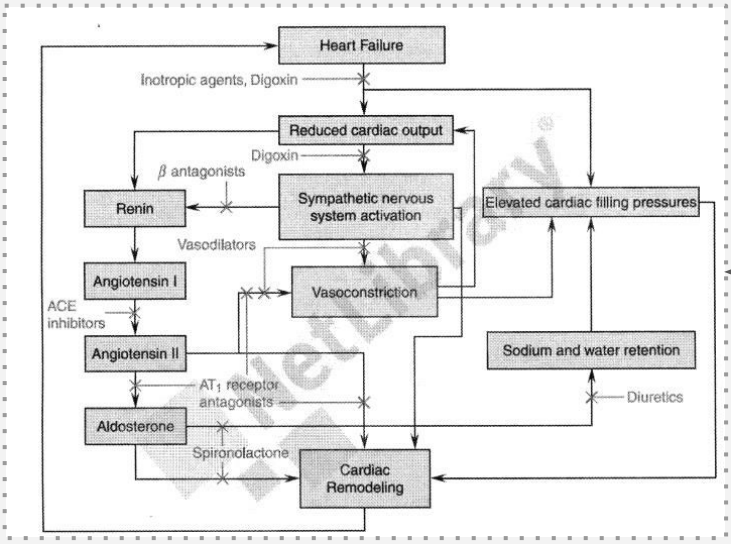
PATHOPHYSIOLOGY OF CHF

When there is low CO it will cause the heart to undergo compensatory responses*

Factors affecting cardiac output and heart failure:
1-Preload.
2-Afterload.
3-Cardiac contractility.



Drugs used in treatment of HF



Site of drug action

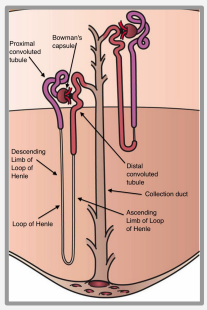
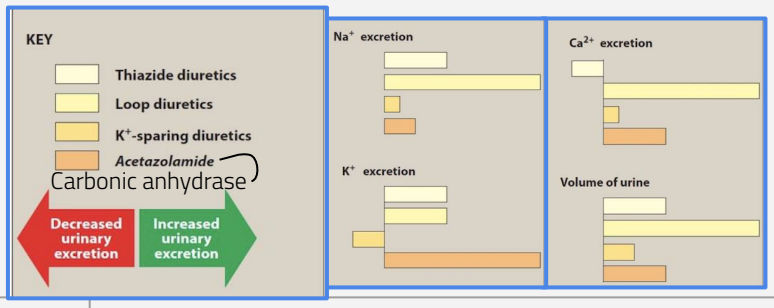
I- Drugs that decrease preload:	
1 - Diuretics	Chlorothiazide , Furosemide
2 - Aldosterone antagonists	Spironolactone, Eplerenone
3 - Venodilators	Nitroglycerine, Isosorbide dinitrate
II- Drugs that decrease afterload:	
1 - Arteriodilators	Hydralazine
III- Drugs that decrease both preload & afterload: **(Combined arteriolo- & venodilators)**	
1- Angiotensin converting enzyme (ACE) inhibitors	Captopril, Enalapril, Ramipril
2- Angiotensin receptor antagonists	Losartan, Valsartan, Irbesartan
3- α1-adrenoceptor antagonists	Prazosin
4- Direct vasodilators	Sodium nitroprusside
IV- Drugs that increase heart contractility:	
1- Cardiac glycosides (digitalis)	Digoxin
2- β- adrenoceptor agonists	Dobutamine
3- Phosphodiesterase inhibitors	Milrinone, Enoximone, Vesnarinone
β-adrenoceptor blockers in heart failure	
Second generation	Bisoprolol, Metoprolol
Third generation	Carvedilol, Nebivolol
New drugs for heart failure	
Natriuretic Peptides	Nesiritide
Calcium sensitisers	Levosimendan

1-Drug that decrease Preload:

1. Diuretics
2. Aldosterone antagonists
3. Venodilators

Diuretics (↓congestion & edema)

(5 types: thiazides, loop,potassium sparing,carbonic anhydrase inhibitors,osmotic)

drug	Chlorothiazide	★ Furosemide (lasix)
*The girls' were asked to add to their slides what's pink in this slide **M.O.A In HF**	-reduce salt and water retention(↑excretion)→ decrease ventricular preload and venous pressure → reduction of cardiac size → Improvement of cardiac performance. -different diuretics function on different parts of a nephron of the kidney, and because each part is responsible for a certain percentage of salt & water excretion, the part a diuretic drug functions on determines how strong it is (its efficacy). Therefore, a drug that works on a part that secretes 60% of salt & water is strong , but a drug that works on a part that secretes 5% is weak.* -a nephron is divided into 4 parts: proximal convoluted tubule→loop of henle→thick ascending limb of loop of henle→distal convoluted tubule.*   	
Subgroup	Thiazides	Loop diuretics
M.O.A	- Works on distal convoluted tubule (secretion of 5% of water & salt). - Not a strong diuretics (mild).*	- Works on Na-K-Cl cotransporter in cells of the thick ascending limb of loop of henle (secretion of 25% of water & salt).* - A potent diuretic.
Use	- First-line agent in heart failure therapy (for edema). - Used in volume overload (Pulmonary and/or peripheral edema) (↓pulmonary congestion). - Used in mild congestive heart failure (in stable cases only).	- Used in emergency. - Used for immediate reduction of pulmonary congestion (edema) & severe edema associated with: 1- Acute heart failure. 2- Moderate & severe chronic failure. -↑ urine output,cause hypotension and hypokalemia. -loop is better than thiazide in HF.
	- Monitor renal function, blood pressure and ion electrolyte.	
ADRs	-↑ urine output,cause hypotension and hypokalemia.	

Aldosterone antagonists & potassium sparing diuretics		
drug	**Spironolactone**	**Eplerenone**
M.O.A	- Non-selective Antagonist of aldosterone receptor. (non-selective means it can bind to other steroid hormones receptors). - A potassium sparing diuretic (K+ is not exerted→ hyperkalemia).	- A new selective aldosterone receptor Antagonist (does not inhibit other hormones such as estrogens & androgens).
Use	Improves survival in advanced heart failure.	- Indicated to improve survival of stable patients with congestive heart failure.

Venodilators		
drug	**Nitroglycerine**	**Isosorbide dinitrate**
PK	- Can be given IV or sublingual.	
M.O.A	-↑cGMP in smooth muscles of vessels→ Dilates venous blood vessels & reduce preload.	
Use	- Used I.V. for severe heart failure when the main symptom is dyspnea due to pulmonary congestion. - Used in emergency.	

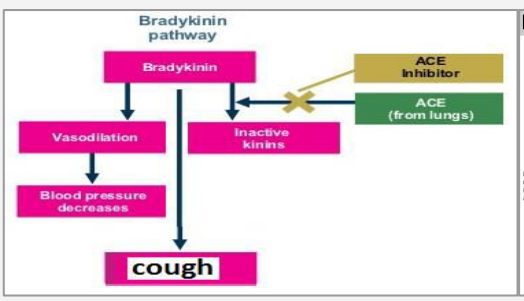
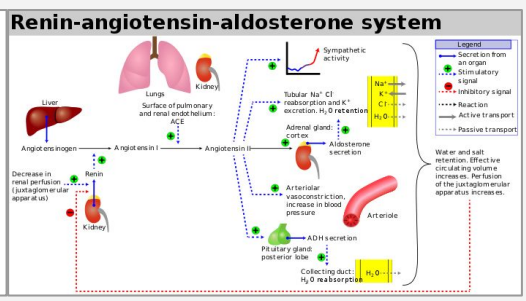
2-Drugs that decrease afterload

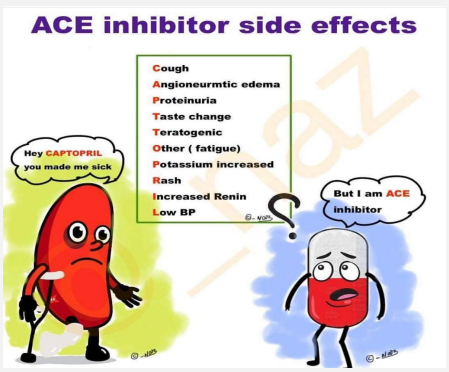
Arteriodilators (mainly used in hypertension & HF while in angina venodilators are mainly used)	
drug	**Hydralazine**
M.O.A	- Direct relaxation of vascular smooth muscle cells in resistance arterioles→ reduce peripheral vascular resistance.
Use	- Used when the main symptom is rapid fatigue due to low cardiac output.
ADRs	Hypotension, lupus-like-syndrome

3-Drugs that decrease both preload and afterload

1	2	3	4
(ACE) inhibitors	(ARBs)	α-Adrenoceptor BLOCKERS	Direct acting vasodilators

Angiotensin converting enzyme (ACE) inhibitors (ACEI)

Drug	Captopril (prototype)	Enalapril	Ramipril
P.K	–	- Prodrugs, converted to their active metabolites in liver. - Have long half-life & given once daily.	
	- Rapidly absorbed from GIT after oral administration. - Food reduce their bioavailability. - Renal excretion.		
RAAS system effects	Plasma protein **Angiotensinogen** (synthesized in the liver) is converted to angiotensin I by renin (enzyme synthesized in juxtaglomerular cells of the kidney & then released in the circulation). While blood flows through the small vessels of the lungs Angiotensin I is converted to Angiotensin II by angiotensin converting enzyme (ACE) that is present in the endothelium of lung blood vessels. **Angiotensin II effects:** ➔ extremely powerful vasoconstrictor (constriction of arterioles→↑ total peripheral resistance→↑arterial pressure) (mild constriction of veins →↑venous return). ➔ stimulating secretion of aldosterone (sodium and water retention). ➔ stimulating secretion of vasopressin (Antidiuretic hormone)→ water retention. ➔ stimulating the sympathetic system. ➔ Causes hypertrophy of vascular & cardiac cells & increases synthesis & deposition of collagen by cardiac fibroblasts (remodeling). - Increased renin in the body is mainly responsible for cardiac & vascular remodeling. - ACE (kininase II) is also essential for the **the breakdown of Bradykinin**.  	
M.O.A	So by inhibiting ACE, we will achieve the opposite of all angiotensin II normal actions in addition to vasodilatation by the accumulation of Bradykinin. This results in increase in CO.		

Pharmacological actions	1- Decrease peripheral resistance (Afterload) (arteriodilation). 2- Decrease Venous return (Preload) (venodilation). 3- Decrease sympathetic activity. 4- Inhibit cardiac and vascular remodeling associated with chronic heart failure → decrease in mortality rate.
Uses	- Considered as first-line drugs for chronic heart failure along with diuretics. - First-line drugs for hypertension therapy.
ADRs	- Acute renal failure (because glomerular filtration & vascular tone are dependent on Ang II), especially in patients with renal artery stenosis. - Hyperkalemia (because aldosterone is inhibited), especially in patients with renal insufficiency or diabetes. - Severe hypotension in hypovolemic patients (they are hypovolemic due to diuretics, salt restriction or gastrointestinal Fluid loss e.g. severe vomiting or diarrhea). - Dysgeusia (reversible loss or altered taste). (reversible: if we stop the drug the side effect will disappear). The last 2 are due to bradykinin accumulation:- - Dry cough sometimes with wheezing (especially captopril). - Angioneurotic edema (swelling in the nose, throat, tongue, larynx → severe issue that must be treated -Dangerous-). 
Contra-indication	- During the second & third trimesters of pregnancy (D category) (due to the risk of : fetal hypotension, renal failure and malformations). - Renal artery stenosis. Table 1. FDA Drug Risk Classification Category / Description A — Controlled studies in humans show no risk to the fetus B — No controlled studies have been conducted in humans; animal studies show no risk to the fetus C — No controlled studies have been conducted in animals or humans D — Evidence of human risk to the fetus exists; however, benefits may outweigh risks in certain situations X — Controlled studies in both animals and humans demonstrate fetal abnormalities; the risk in pregnant women outweighs any possible benefit Source: References 4-7.

Angiotensin receptor blockers (ARBs)	
Drug	**Losartan** **Valsartan** **Irbesartan**
M.O.A	- Block angiotensin 1 (AT1) receptors (angiotensin production is not effected & there is no accumulation of bradykinin). - Decrease action of angiotensin II. - AT1 mediates most of the known actions of Ang & predominate in vascular smooth muscle → renal sodium reabsorption, vasoconstriction, cell growth and proliferation (remodeling). - AT2 → natriuresis, vasodilation, anti proliferation.

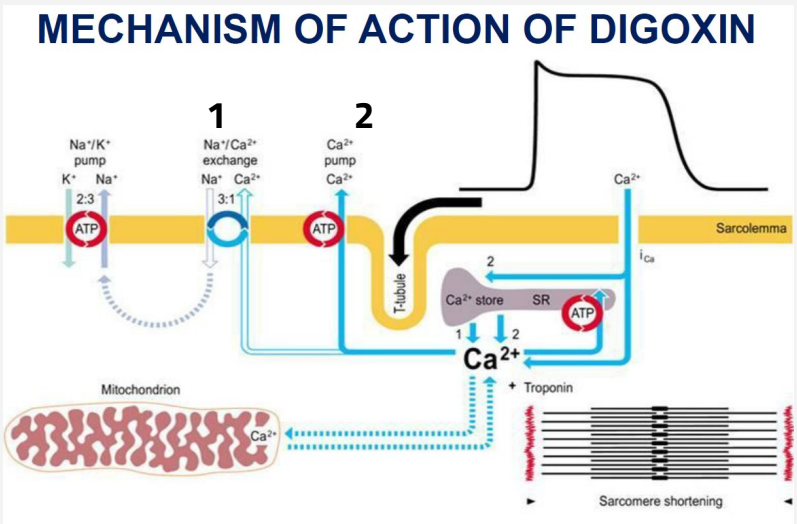
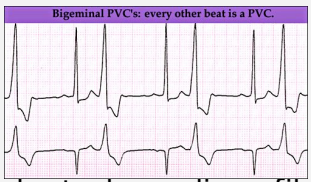
α-Adrenoceptor BLOCKERS	
Drug	**Prazosin**
M.O.A	- blocks α- receptors in arterioles and venules. - decrease both afterload & preload.

Direct acting vasodilators (by ↑ cGMP)	
Drug	**Sodium nitroprusside**
P.K	- Acts immediately and effects lasts for 1-5 min. (it doesn't affect the receptors it acts directly on blood vessels , so the action will be very fast)
Uses	- Given I.V. for acute or severe heart failure used in emergencies

3-Drugs that increase contractility

1. **Cardiac glycosides (digitalis)**
2. **β-Adrenoreceptor AGONIST**
3. **phosphodiesterase-III inhibitors**

Cardiac glycosides (digitalis)

Drug	Digoxin
M.O.A	1- Na+ / K+ ATPase enzyme (the sodium pump)→ Transport 3Na out of & 2K into the heart (cardiomyocyte) against their concentration gradient in the presence of ATP (active ion transporter mechanism). 2- Na+-Ca++ exchanger (Ca→out, Na→in). - Inhibit Na+ / K+ ATPase enzyme (the sodium pump) by binding to K site (so it competes with K for its site) → ↑ intracellular Na→ reversal in the exchange function of Na+-Ca++ exchanger (Na→ out, Ca →in)→↑ intracellular Ca that also ↑ intracellular Ca even further by Calcium-induced calcium release→↑contractility. - Increases the force of myocardial contraction (+ve inotropic effect).  -The girls' were asked to add to their slides what's pink in this slide.
Uses	- Congestive heart failure ONLY if patient has decrease in contractility (438). - Has narrow therapeutic index.
ADRs	**-Cardiac:** **digitalis-induced arrhythmias:** - Extrasystoles. - Coupled beats (Bigeminal rhythm).  - Ventricular tachycardia or fibrillation. - Cardiac arrest (toxic dose). **-non-cardiac:** -**GIT:** anorexia (loss of appetite), nausea, vomiting, diarrhea -**CNS:** headache, visual disturbances, drowsiness.
Factors that increase its toxicity (check for ion balance before starting therapy)	- Renal diseases (because it's excreted through it & because the kidney is responsible for ion balance in the body and any imbalance in ions will affect digoxin toxicity). - Hypokalemia (could happen by taking diuretics, ↓K so easier binding of digoxin). - Hypomagnesemia (Mg is cofactor of sodium pump so if it not present the pump won't function achieving what digoxin is already trying to achieve). - Hypercalcemia (↑↑ intracellular Ca).

β-Adrenoreceptor AGONIST	
Drug	**Dobutamine**
M.O.A	Selective β1 agonist
Uses	Treatment of acute heart failure in cardiogenic shock

phosphodiesterase-III inhibitors		
Drug	**Milrinone**	**Enoximone & Vesnarinone**
M.O.A	Inhibits phosphodiesterase -III (cardiac & B. Vessels)⟶↑cAMP. -↑cAMP in cardiomyocytes⟶Increases cardiac contractility. -↑cAMP in vascular smooth muscles⟶Dilatation of arteries & veins (reduction of preload & afterload).	
Uses	- Used in emergency. - Used only IV for management of acute heart failure. - Not safe or effective in the longer (> 48 hours) treatment of patients with heart failure (many side effects after 48 h).	New drugs in clinical trials
ADRs	- Hypotension and chest pain (angina).	_
Chemical interactions	- Furosemide should not be administered in I.V. lines containing milrinone due to formation of a precipitate (It affects their absorption because they have to be in a dissolved form to be absorbed).	-

The use of β-adrenoreceptor blockers in heart failure

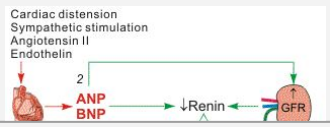
<table>
<tr><th colspan="4">β-adrenoreceptor blockers</th></tr>
<tr><td colspan="4">-The chronic elevated adrenergic activity in chronic heart failure patients cause structural remodeling of the heart (cardiac dilatation & hypertrophy).</td></tr>
<tr><td rowspan="2">generations</td><td>Second generation</td><td colspan="2">Third generation</td></tr>
<tr><td rowspan="2">Cardioselective
(β1-receptors)</td><td colspan="2">Beta blockers with additional cardiovascular actions</td></tr>
<tr><td>Non selective vasodilators (mixed alpha and beta blocker)(α1,β1, β2)(selective α and non selective β-blocker)

β1-receptors blocker + have vasodilator actions(α blocking effect)</td><td>β1-selective with vasodilating properties not mediated by α blockade but due to increase in endothelial release of NO via induction of eNOS.</td></tr>
<tr><td>drugs</td><td>E.g:
Bisoprolol
Metoprolol</td><td>E.g:
Carvedilol</td><td>E.g:
Nebivolol</td></tr>
<tr><td>M.O.A in HF</td><td colspan="3">1- Attenuate تقلل من cardiac remodeling.
2- Slow heart rate, which allows the left ventricle to fill more completely.
3- Decrease renin release (thats why its protective against remodeling)
→reduce mortality & morbidity of patients with HF</td></tr>
<tr><td>use</td><td colspan="3">-Reduce the progression of CHRONIC heart failure.
-NOT used in ACUTE heart failure.</td></tr>
</table>

New drugs for heart failure

1 **Natriuretic Peptides**

2 **Calcium sensitisers**

Natriuretic Peptides	
Drug	**Nesiritide**
Definition	A purified preparation of human BNP, manufactured by recombinant DNA technology (it's BNP administered as a drug). - BNP (Brain Natriuretic Peptide) is a hormone secreted by cardiomyocyte in the heart ventricles in response to stretch caused by increased ventricular blood volume. - ANP (Atrial Natriuretic Peptide) is a hormone secreted by the atria as a response to atrial distension (also by ventricles as heart failure advances). - Elevated BNP and ANP are associated with advanced HF (it is a compensatory mechanism of the heart in heart failure).
M.O.A	• Physiological effects of ANP and BNP: - Vasodilation. - Natriuresis (excretion of sodium in urine). - Inhibition of RAAS (inhibitory effects on renin secretion, inhibit the actions of ANG II & aldosterone). -↑ Cyclic-GMP in vascular smooth muscle leading to : - Smooth muscle relaxation (vasodilation). - Reduction of preload and afterload. - Diuretic effects. 
Uses	Indicated (IV) for the treatment of patients with (ADHF) who have dyspnea at rest or with minimal activity (not given in stable cases).

❖ **Acute Decompensated Heart Failure (ADHF)**: A sudden worsening of the signs and symptoms of heart failure, which typically includes:
1-dyspnea 2-leg or feet swelling 3-fatigue

- ADHF is a common and potentially serious cause of respiratory distress.

Calcium sensitisers	
Drug	**Levosimendan**
M.O.A	- Calcium sensitization (improves cardiac contractility **WITHOUT** increasing oxygen consumption) (no extra work on heart). - Potassium-ATP channel opening (cause vasodilation, improving blood flow to vital organs). ADHF=Acute decompensated heart failure -These effects reduce the risk of worsening ADHF or death compared with dobutamine.
Uses	Used in management of ADHF (not given in stable cases).

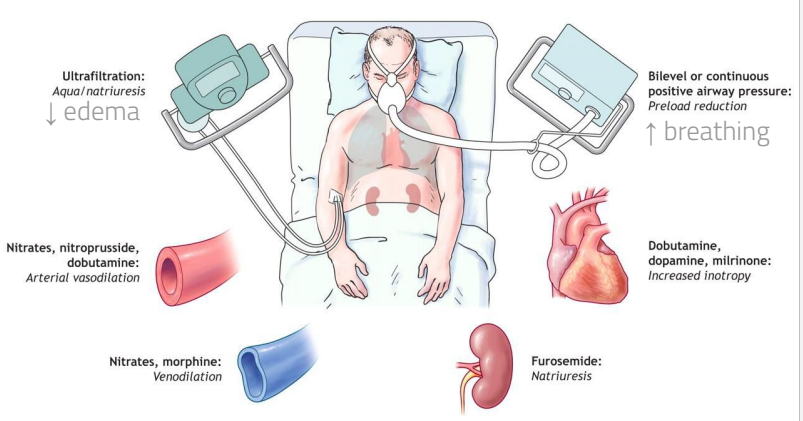
Non-pharmacological **management of Chronic Heart Failure**

- Reduce workload of the heart:

  - Limit patient activity
  - Reduce weight
  - Control hypertension

- Restrict sodium (because ↑Na ⟶ ↑BP⟶↑edema).
- Stop smoking.

management of acute Heart Failure



heart failure functional Classification and management of Chronic Heart failure

The severity of heart failure is usually described according to a scale devised by the New York Heart Association (NYHA):

NYHA Class:	Symptoms	For Survival/Morbidity	For Symptoms
I	Cardiac disease, but no symptoms & no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc. -symptoms occur only with greater than ordinary exercise.	Continue ACE inhibitor/ARB if ACE inhibitor intolerant, continue aldosterone antagonist if post-MI and add beta-blocker if post MI.	Reduce / stop diuretic (if there's no edema)
II	Mild symptoms (mild shortness of breath &/or angina), slight limitation during ordinary activity which result in fatigue and palpitation.	ACE inhibitor as first-line treatment/ARB if ACE inhibitor intolerant add beta blocker and aldosterone antagonist if post-MI	+/- Diuretic depending on fluid retention
III	Marked limitation in activity due to symptoms (fatigue,etc), even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest (no symptoms).	ACE inhibitor + ARB or ARB alone if ACE intolerant beta-blocker add aldosterone antagonist	+ Diuretics + Digitalis If still symptomatic
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bed bound patients	Continue ACE inhibitor/ARB beta blocker aldosterone antagonist	+Diuretics +Digitalis +Consider temporary inotropic support

- The New York Heart Association (NYHA) Classification of the extent of heart failure based on their limitations during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain+DR.note:dyspnea,palpitation,fatigue,physical activity of patient.
- ACE intolerant means has contraindication or intolerable side effects.
- Cardiac remodeling mediators⟶ aldosterone,angiotensin,sympathetic.
- Improve symptoms⟶ diuretics,digitalis
- 3 main drugs used (all ↓ remodeling & compensatory mechanism)
1st: ACEI and ARB.
2nd: β blockers(↓mortality)
3rd:aldosterone antagonists(↓mortality)
- Our strategy with HF: 1-elevate symptoms,2-slow disease progression.

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 patients intolerant to ACE inhibitors & ARBs due to renal dysfunction.

MCQ

1-Primarily an arterial vasodilator that reduces peripheral vascular resistance in heart failure:			
A-Nitroglycerine	B- Hydralazine	C-Eplerenone	D-Isosorbide

2- Which drug has narrow therapeutic index			
A-Dobutamine	B-Milrinone	C-Vesnarinone	D-Digoxin

3- A 69 years old women has been admitted to the coronary care unit with a left ventricular myocardial infarction. She develops acute severe heart failure with marked pulmonary edema, but no evidence of peripheral edema. Which one of the following drugs would be most useful.			
A-digoxin	B-minoxidil	C-furosemide	D-propranolol

4- A 37 years old Asian man was diagnosed with Acute Decompensated Heart Failure, Which one of the following drugs would be most useful			
A-digoxin	B-Nesiritide	C-Eplerenone	D-Milrinone

5-A 63-year-old man with congestive heart failure comes to the cardiologist for a routine visit. He is doing well and has no complaints. He is taking digoxin, metoprolol, and spironolactone. What is the mechanism of action of spironolactone?			
A-Aldosterone receptor antagonist	B-Inhibit Na+ / K+ ATPase enzyme	C-Inhibits phosphodiesterase -III	D-Calcium sensitization

6-A 60-year-old woman suffers an anterior wall myocardial infarction. She recovers well initially but soon develops left heart failure. Her physician prescribes multiple medications to treat different aspects of heart failure, including isosorbide dinitrate. What is the mechanism of action of this agent?			
A-Causes excess fluid elimination	B-Inhibits production of angiotensin II	C-Reduces preload	D-Increases cardiac inotropy

Answers

1	2	3	4	5	6
B	D	C	B	A	C

SAQ

Q1) What's the drug that has been shown to reduce mortality rate in chronic heart failure?

Q2) What is the M.O.A of ACE Inhibitor?

Q3) What are the factors that increase toxicity of Digoxin?

Q4) Mention the Non-pharmacological management of Chronic Heart Failure.

Q5) Mention the therapy of african americans with congestive heart failure.

Q6) What is β-adrenoreceptor blockers MOA in heart failure?

Answers

A1) Spironolactone, beta blockers, ACE inhibitors.

A2) The drug will inhibit ACE enzyme → inhibiting formation of Angiotensin II (a vasoconstrictor) and inhibiting the breakdown of bradykinin (a potent vasodilator) → ↓ preload & afterload

A3) Renal diseases - Hypokalemia - Hypomagnesemia - Hypercalcemia

A4) Stop smoking-Restrict sodium-Control Hypertension-Reduce Weight-Limit patient activity.

A5) Addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy.

A6) 1- Slow heart rate, which allows the left ventricle to fill more completely.
2- Attenuate cardiac remodeling.
3- Decrease renin release → reduce mortality & morbidity of patients with HF

GOOD LUCK!

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