MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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Drugs for heart failure

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

OBJECTIVES:

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

✓Describe the different classes of the drugs used for treatment of acute & chronic heart failure & their mechanism of action

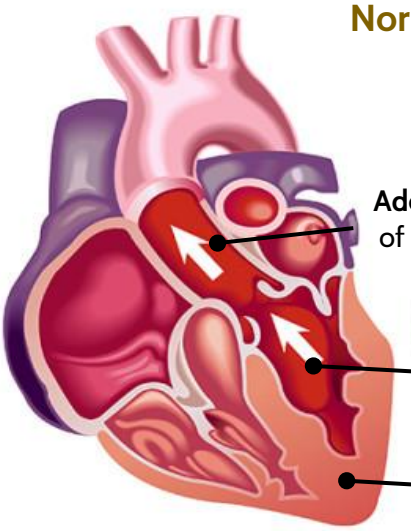
✓understand their pharmacological effects, clinical uses, adverse effects & their interactions with other drugs .

Editing File

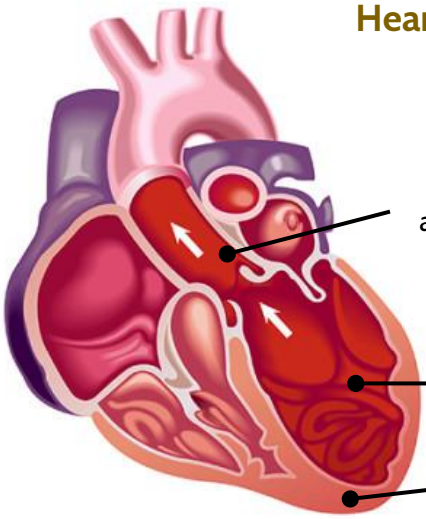
What is Heart failure?

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

Normal Heart



Heart Failure

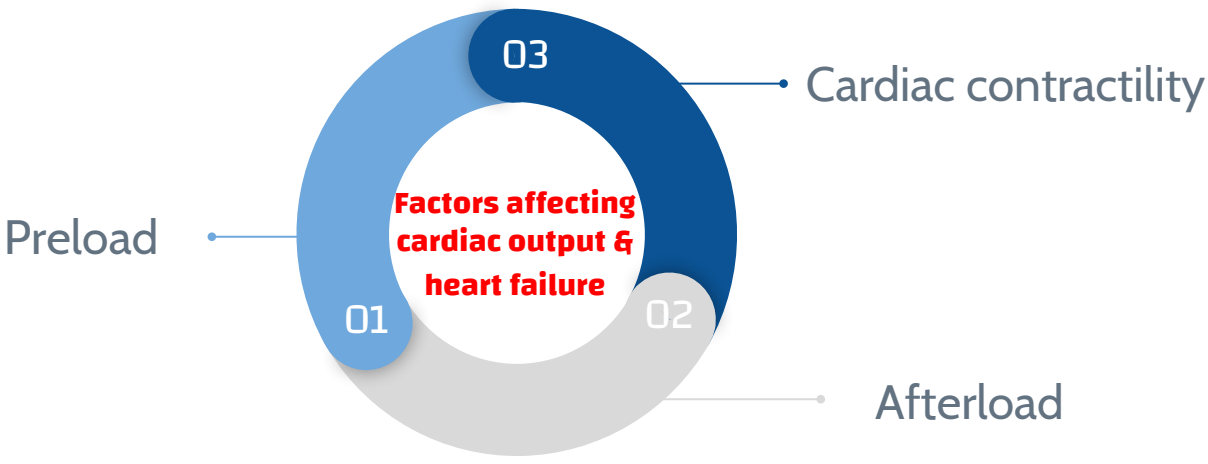


Symptoms:

- Tachycardia
- Peripheral edema
- Cardiomegaly
- Dyspnea
  (Pulmonary congestion)
- Decrease exercise tolerance
  (Rapid fatigue).

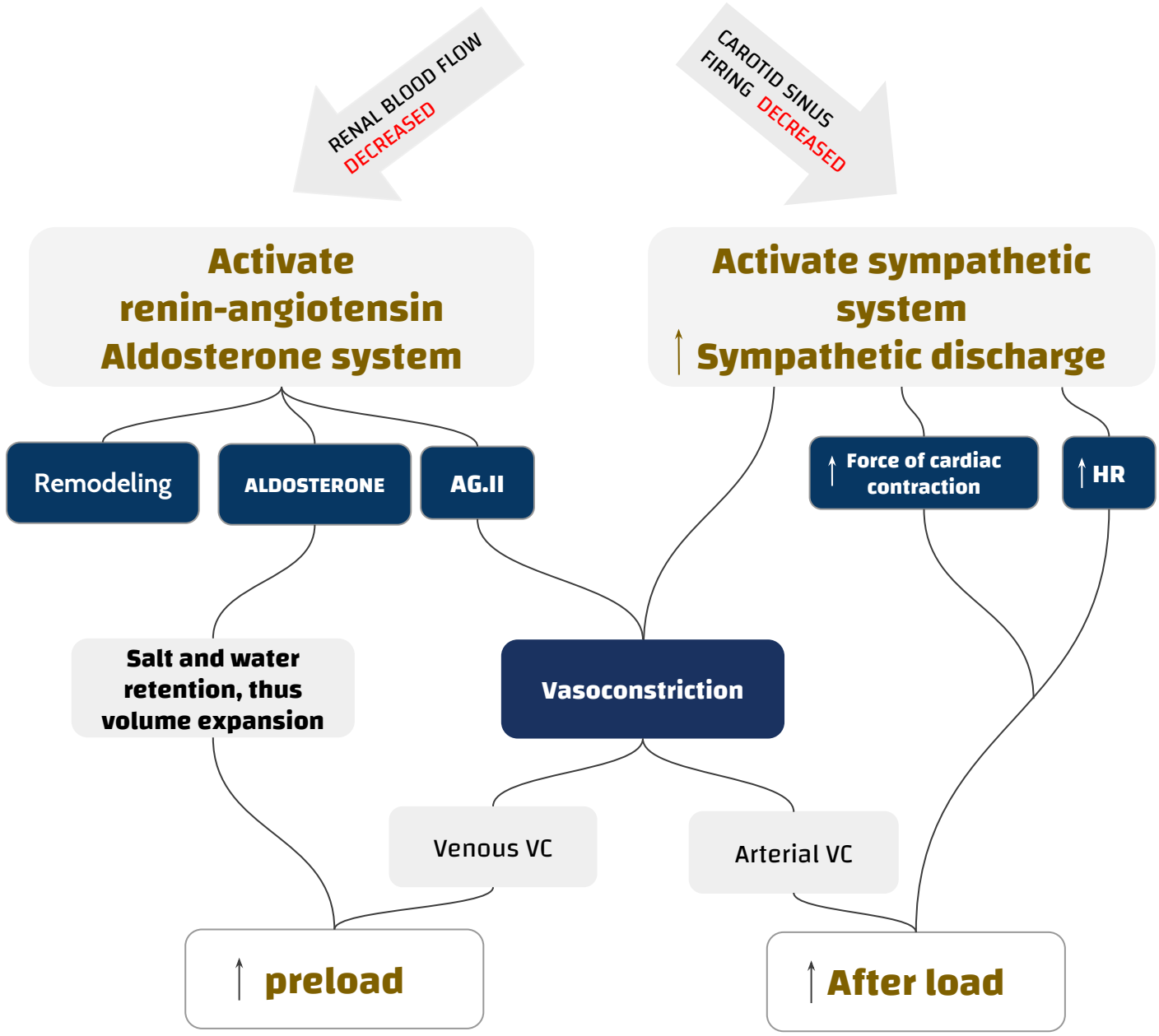
Causes:

- Heart valve disorder
- Abnormal heart rhythm
  "if it's not treated it will cause HF"
- High blood pressure
- Disorder of coronary arteries
- Cardiomyopathy



Pathophysiology of CHF:

when the force of contraction is reduced it will lead to low cardiac output "CO= HR* stroke volume"



Drugs used in treatment of heart failure (overview):

I- drugs that decreases preload

a- Diuretics.

b- Aldosterone antagonist

c- Venodilators

II - drugs that decreases afterload

a- Arteriodilators

III - drugs that decreases both pre & after load

a- Angiotensin converting enzyme (ACE) inhibitors

b- Angiotensin receptor antagonists

c- α_1-adrenoceptor antagonist

d- Direct vasodilators

IV - drugs that increases heart contractility

a- Cardiac glycosides (digitalis)

b- β- adrenoceptor agonists

c- Phosphodiesterase inhibitors

Drugs used in treatment of heart failure

Drug that decrease Preload:

1. Diuretics
2. Aldosterone antagonists
3. Venodilators

1) Diuretics

Drug	Chlorothiazide "Act on distal convoluted tubules which are responsible of only 5% of the reabsorption".	Furosemide "more potent, works on some segments in the kidney which are responsible of 25% of reabsorption"
M.O.A	reduce salt and water retention →decrease ventricular preload and venous pressure →reduction of cardiac size → Improvement of cardiac performance .	
Use	-first-line agent in heart failure therapy. -Used in volume overload (Pulmonary and/or peripheral edema) -Used in mild congestive heart failure.	-a potent diuretic. USED IN EMERGENCIES -used for immediate reduction of pulmonary congestion & severe edema associated with: 1-acute heart failure 2- moderate & severe chronic failure.

2) Aldosterone antagonists

Drug	Spironolactone	Eplerenone
M.O.A	-Non selective Antagonist of aldosterone receptor. "it is not selective for this hormone receptor and it may bind to other steroid hormones receptors' " -A potassium sparing diuretic. K^+ is not exerted	-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.

3) Venodilators

Drug	• Nitroglycerin • Isosorbide dinitrate
M.O.A	Dilates venous blood vessels and reduce preload .
Use	-Used I.V for severe heart failure when the main symptom is dyspnea due to pulmonary congestion.

Drugs that decrease Afterload:

1. Arteriodilators

1) Arteriodilators

Drug	Hydralazine
M.O.A	Reducing peripheral vascular resistance
Use	Used when the main symptom is rapid fatigue due to low cardiac output

Drugs that decrease both preload and afterload
(Combined arteriolo- & venodilators)

1. ACE inhibitors
2. Angiotensin receptor antagonists
   "commonly used in hypertension"
3. α-adrenoceptor antagonists
4. Direct-acting vasodilators

1) Angiotensin Converting Enzyme (ACE) inhibitors

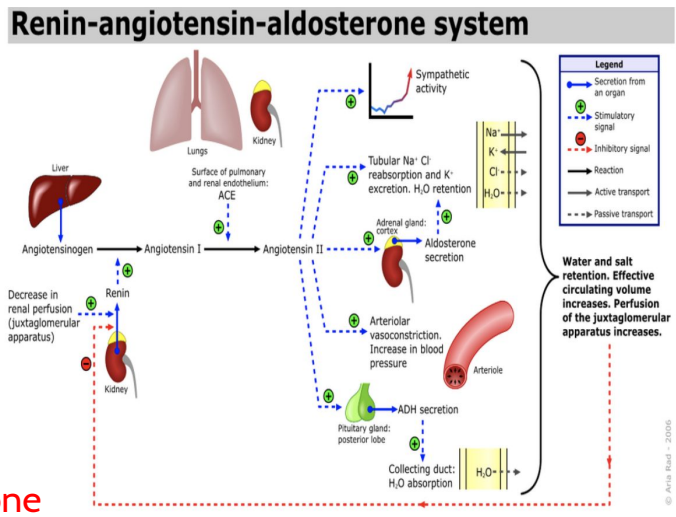
Drug	Captopril	Enalapril	Ramipril
P.K	-rapidly absorbed from GIT after oral administration -food reduce their bioavailability		
	-	-They are prodrugs, converted to their active metabolites in liver. -have long half-life & given once daily.	
M.O.A	The drug will inhibit ACE enzyme = inhibiting formation of Angiotensin II (a vasoconstrictor) and inhibiting the breakdown of bradykinin (a potent vasodilator) "the accumulation of bradykinin have some side effects will be discussed below" =↓ preload & afterload		
Action	Decrease in mortality rate by: -Decrease peripheral resistance (Afterload) -Decrease Venous return (Preload) -Decrease sympathetic activity -Inhibit cardiac and vascular remodeling associated with chronic heart failure		
Uses	-Considered as first-line drugs for chronic heart failure along with diuretics - First-line drugs for hypertension therapy		
ADRs	-acute renal failure, especially in patients with renal artery stenosis. -hyperkalemia, especially in patients with renal insufficiency or diabetes. -severe hypotension in hypovolemic patients due to diuretics, salt restriction or gastrointestinal fluid loss like vomiting or diarrhea. All the 3 below are due to bradykinin accumulation ; -dry cough sometimes with wheezing -angioneurotic edema (swelling in the nose, throat, tongue, larynx). -dysgeusia (reversible loss or altered taste).		
Contra-indications.	-during the second & third trimesters of pregnancy,due to the risk of : fetal hypotension,renal failure & malformations. -renal artery stenosis.		

The edited part

Mechanism of Action of ACE Inhibitors:

In the plasma we have a protein called **Angiotensinogen** which is synthesized in the liver. When **Renin is secreted from the kidneys**, it will convert *Angiotensinogen* to *Angiotensin I* which then goes to the lungs to be *converted to Angiotensin II* BY **"Angiotensin Converting Enzymes (ACE)"**
Angiotensin II has many physiological effects such as:

- ➔ severe vasoconstriction
- ➔ stimulating secretion of aldosterone
- ➔ stimulating secretion of vasopressin
- ➔ stimulating the sympathetic system



-ACE is also essential for the **the breakdown of Bradykinin.**

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.

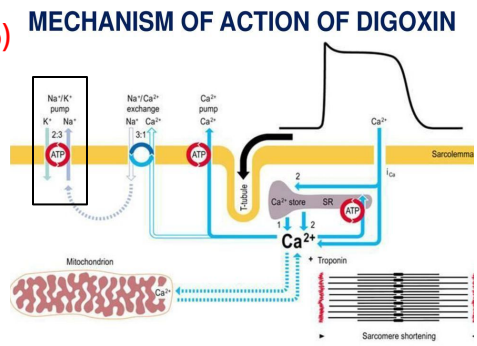
Drugs that decrease both preload and afterload (CONT)

	2) Angiotensin receptor blockers ARBs "antagonists".	3) α- adrenoceptor blockers "antagonists".	4) Direct-acting vasodilators
Drug	• Losartan • Valsartan • Irbesartan	Prazosin	Sodium nitroprusside
M.O.A	-Block AT1 receptors. -Decrease action of Angiotensin II.	-Blocks α- receptors in arterioles and venules. -Decrease both preload and afterload.	-Acts immediately and effects lasts for 1-5 mins.
Uses	—		-Given IV for acute or severe heart failure. used in emergencies

Drugs that increase contractility

1. Cardiac glycosides (digitalis)
2. β-Adrenoreceptor agonist
3. Phosphodiesterase-III inhibitors

1) Cardiac glycosides (digitalis)

Drug	Digoxin	
M.O.A	- Inhibit Na+/K+ ATPase enzyme (the sodium pump) - Increase the force of myocardial contraction (+ve inotropic effect) This drug inhibits Na+/k+ pump so due to Na+ accumulation in the cell the Na+/ca++ pump will be activated in reverse. moving 3 Na+ out and bringing 1 Ca++ in, so this will increase Ca++ concentration inside the cell thus, increases the force of contraction. 	
Uses	- Congestive heart failure ONLY if patient has decrease in contractility. - Has narrow therapeutic index	
ADRs toxic doses	(Cardiac) CVS: **Digitalis-induced arrhythmias:** -extrasystoles -coupled beats (Bigeminal rhythm) -ventricular tachycardia or fibrillation -**cardiac arrest**	(Non-cardiac) Warning sign GIT: anorexia, nausea, vomiting, diarrhea. CNS: headache, visual disturbances, drowsiness. we should inform the patient about these ADRs, so we can treat the toxicity early.
Factors that increase its toxicity:	-Renal diseases -Hypokalemia "because k+ compete with digoxin on Na+/k+ pump so when it is reduced inhibiting the pump will be easier " -Hypomagnesemia "mg is a cofactor for Na+\k+ pump" -Hypercalcemia	

2) β-adrenoreceptor AGONIST

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

Drugs that increase contractility (CONT)

3) Phosphodiesterase-III inhibitors

Drug	Milrinone	Enoximone & Vesnarinone
M.O.A	Inhibits phosphodiesterase-III (cardiac & Blood Vessels) thus : "increase cAMP" - Increases cardiac contractility - Dilatation of arteries & veins (reduction of preload & afterload) additional beneficial effect.	-
Uses	- Used only IV for management of **acute heart failure** **- Not safe or effective in the longer (> 48 hours)** Treatment of patients with heart failure	New drugs in clinical trials.
ADRs	- Hypotension and chest pain (angina) - **Chemical interaction**: **Furosemide** should not be administered in I.V. lines containing milrinone due to formation of a precipitate	-

The use of β-adrenoreceptor blockers in heart failure

The elevated adrenergic activity in chronic heart failure patients cause structural remodeling of the heart (cardiac dilatation & hypertrophy)

What β-blockers do

-Reduce the progression of CHRONIC heart failure.

- NOT used in ACUTE heart failure

Mechanism of action

- Attenuate cardiac remodeling.
- Slow heart rate, which allows the left ventricle to fill more completely.
- Decrease renin release , thus:

reduce mortality & morbidity of patients with HF

Generations

- Second generation: cardioselective (β1 -receptors) **e.g:** Bisoprolol, Metoprolol
- Third generation: β1-receptors blocker + have **vasodilator actions** (α blocking effect) **e.g:** Carvedilol, Nebivolol

They are commonly used

New drugs for heart failure

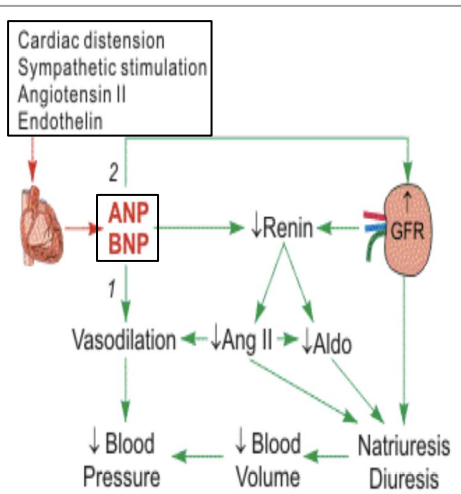
1 Natriuretic Peptides

2 Calcium sensitisers

	*Natriuretic Peptides	Calcium sensitisers
Drug	Nesiritide	Levosimendan
Definition	A purified preparation of human BNP, manufactured by recombinant DNA technology	-
M.O.A	BNP and ANP are secreted NATURALLY by heart in response to heart stretch. BNP = Ventricles stretch ANP= atrial stretch it is a compensatory mechanism of the heart in heart failure. elevated BNP and ANP are associated with advanced HF. ↑ Cyclic-GMP in vascular smooth muscle leading to : 1- Smooth muscle relaxation 2- Reduction of preload and afterload	- Calcium sensitization (improves cardiac contractility **WITHOUT** increasing oxygen consumption) - Potassium-ATP channel opening (cause vasodilation, improving blood flow to vital organs) These effects reduce the risk of worsening ADHF or death compared with dobutamine.
Uses	Indicated (IV) for the treatment of patients with **Acute Decompensated Heart Failure (ADHF)** who have dyspnea at rest or with minimal activity.	Used in management of ADHF

*Natriuretic Peptides:

- BNP is secreted by the ventricles in response to stretch
- elevated BNP is associated with advanced heart failure (compensatory mechanism in HF)



**Acute Decompensated Heart Failure (ADHF)

A sudden worsening of the signs & symptoms of heart failure, which typically includes:
● difficulty breathing (dyspnea) ● leg or feet swelling ● fatigue.
ADHF is a common & potentially serious cause of acute respiratory distress.

Classification & Management of Chronic HF

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.	Continue ACE inhibitor/ARB if ACE inhibitor intolerant, continue aldosterone antagonist if post-MI and add beta-blocker.	Reduce / stop diuretic
II	Mild symptoms (mild shortness of breath &/or angina), slight limitation during ordinary activity	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, even during less than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest	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

- Reduce workload of the heart:
  - Limit patient activity
  - Reduce weight
  - Control hypertension
- Restrict sodium
- Stop smoking

Chronic HF
"Advices for the patients"

Acute HF

- **Continuous positive airway pressure (Ventilation):** to decrease preload.
- **Ultrafiltration,Furosemide :** natriuresis.
- **Nitrates,Nitroprusside , Dobutamine:** Arterial vasodilation
- **Dobutamine,dopamine , Milrinone:** Increase inotropy
- **Nitrate , Morphine:** Venodilation

Congestive Heart Failure in Black Patients

Hydralazine "Arterial Dilators"/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. drug of choice for patients with renal dysfunction.

Summary

Drug	Group		Uses
Chlorothiazide	Drugs that decrease preload	Diuretic	- first-line agent in heart failure therapy - Volume overload (Pulmonary and/or peripheral edema) - Mild congestive heart failure.
Furosemide			- Potent diuretic. -Immediate reduction of pulmonary congestion & severe edema associated with: 1-acute heart failure 2- moderate & severe chronic failure.
Spironolactone		Aldosterone antagonists	-Non Selective - Improves survival in advanced heart failure.
Eplerenone			-Selective - Indicated to improve survival of stable patients with congestive heart failure
• Nitroglycerin • Isosorbide dinitrate		Venodilators	- Used I.V for severe heart failure when the main symptom is dyspnea due to pulmonary congestion
Hydralazine	**Drugs that decrease afterload** Arteriodilators		when the main symptom is rapid fatigue due to low cardiac output
Captopril	Drugs that decrease both preload and afterload	ACE inhibitors	- First-line drugs for chronic heart failure along with diuretics - First-line drugs for hypertension therapy
Enalapril			
Ramipril			
• Losartan • Valsartan • Irbesartan		Angiotensin receptor antagonists	_____
Prazosin		α- adrenoreceptor antagonists	
Sodium nitroprusside		Direct-acting vasodilators	Given I.V for acute or severe heart failure

Summary (CONT)

Drug	Group		Uses
Digoxin	Drugs that increase contractility	Cardiac glycosides (digitalis)	- Congestive heart failure ,only if patient has decrease in contractility. - Narrow therapeutic index
Dobutamine		β-adrenoreceptor agonist	- Treatment of acute heart failure in cardiogenic shock.
Milrinone		Phosphodiesterase-III inhibitors	- used only I.V for management of acute heart failure - Not safe or effective in the longer (> 48 hours) Treatment of patients with heart failure
Enoximone & Vesnarinone			———
Nesiritide	New drugs for heart failure	Natriuretic Peptides	Treatment of patients with Acute Decompensated Heart Failure (ADHF) who have dyspnea at rest or with minimal activity.
Levosimendan		Calcium sensitisers	Management of ADHF

QUIZ

MCQ

1- Which of the following is important to monitor in patients taking digoxin?

A-chloride B-potassium C-sodium

2- Which one of the following describes the mechanism of action of Losartan in Heart failure?

A-Decrease intracellular calcium B-block AT1 receptors C-Decrease cAMP

3- Which one of the statements best describes the action of ACE inhibitors on the failing heart?

A-increase vascular resistance B-decrease cardiac output C-reduce preload

4- A patient is newly diagnosed with HFrEF and is asymptomatic. Which is the most appropriate drug to initiate for symptomatic and survival benefits? HFrEf= heart failure with reduced ejection fraction.

A-Dobutamine B-Furosemide C-ACE inhibitors

5- Beta blockers improve cardiac function in heart failure by?

A-Decrease cardiac remodeling B-Increase heart rate C-Increase renin release

1-B 2-B 3-C 4-C 5-A

SAQ

1-2.SC is a 75-year-old white male who has HF. He is seen in clinic today, reporting shortness of breath, increased pitting edema, and a 5-pound weight gain over the last 2 days. His current medication regimen includes losartan and metoprolol succinate. SC has no chest pain and is deemed stable for outpatient treatment.

Q1.Which management is the best recommendation?

Q2.What is the mechanism of action of that drug?

3-4.During your morning assessment of a 59-year-old patient with heart failure, the patient complains of sudden vision changes that include seeing yellowish-green halos around the lights.

Q3.Which medication do you suspect is causing this issue?

Q4.What is important to monitor in patients taking that drug?

Q5.Describe the mechanism of action of milrinone in HF?

Q1.Furosemide ,

Q2.-reduce salt and water retention → decrease ventricular preload and venous pressure,
→reduction of cardiac size → Improvement of cardiac performance

Q3.Digoxin ,

Q4.Potassium

Q5.increases cardiac contractility

pharmacology

Team 438

GOOD LUCK

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Share with us your ideas !