

Drug therapy of congestive heart failure

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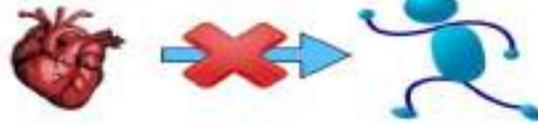


Objectives

- 1- List major drug groups used in treatment of heart failure
- 2- Describe the clinical implications of diuretics, vasodilators, ACE inhibitors and other drugs that lack positive inotropic effects in heart failure
- 3- Ivabredine and ARNIs
- 4- SGLT-2 Inhibitors: dapagliflozin, empagliflozin
- 5- Explain mechanism of action of digitalis and its major effects
- 6- Explain the nature and mechanism of digitalis toxic effects
- 7- Describe the strategies used in the treatment of heart failure
- 8- Approach to management of HF

What is heart failure?

• Inability of the **heart** to maintain **sufficient cardiac output** in spite of **good venous return**



• Heart failure (HF) is a **complex clinical syndrome (not a disease)** that can result from any **structural** or **functional** cardiac disorder that impairs the ability of the **ventricle** to **fill** with or **eject** blood.

Types of HF according to ejection fraction ($EF = \frac{SV}{EDV}$):

Systolic HF: HFrEF

Diastolic HF: HFpEF

Causes of HF (classification)

Etiology	Left-sided HF	Right-sided HF
Increased preload	AR, MR, VSD, hyperdynamic circulation	TR, PR, VSD, hyperdynamic circulation
Increased afterload	AS, Aortic coarctation, systemic hypertension	PS, Pulmonary hypertension, COPD
Decreased contractility	Coronary ischemia, cardiomyopathy, myocarditis	

Drug-induced HF

**Alcoholism and
drug abuse**

**Calcium channel
blockers**

**Potassium
supplements and
other drugs
associated with
hyperkalemia**

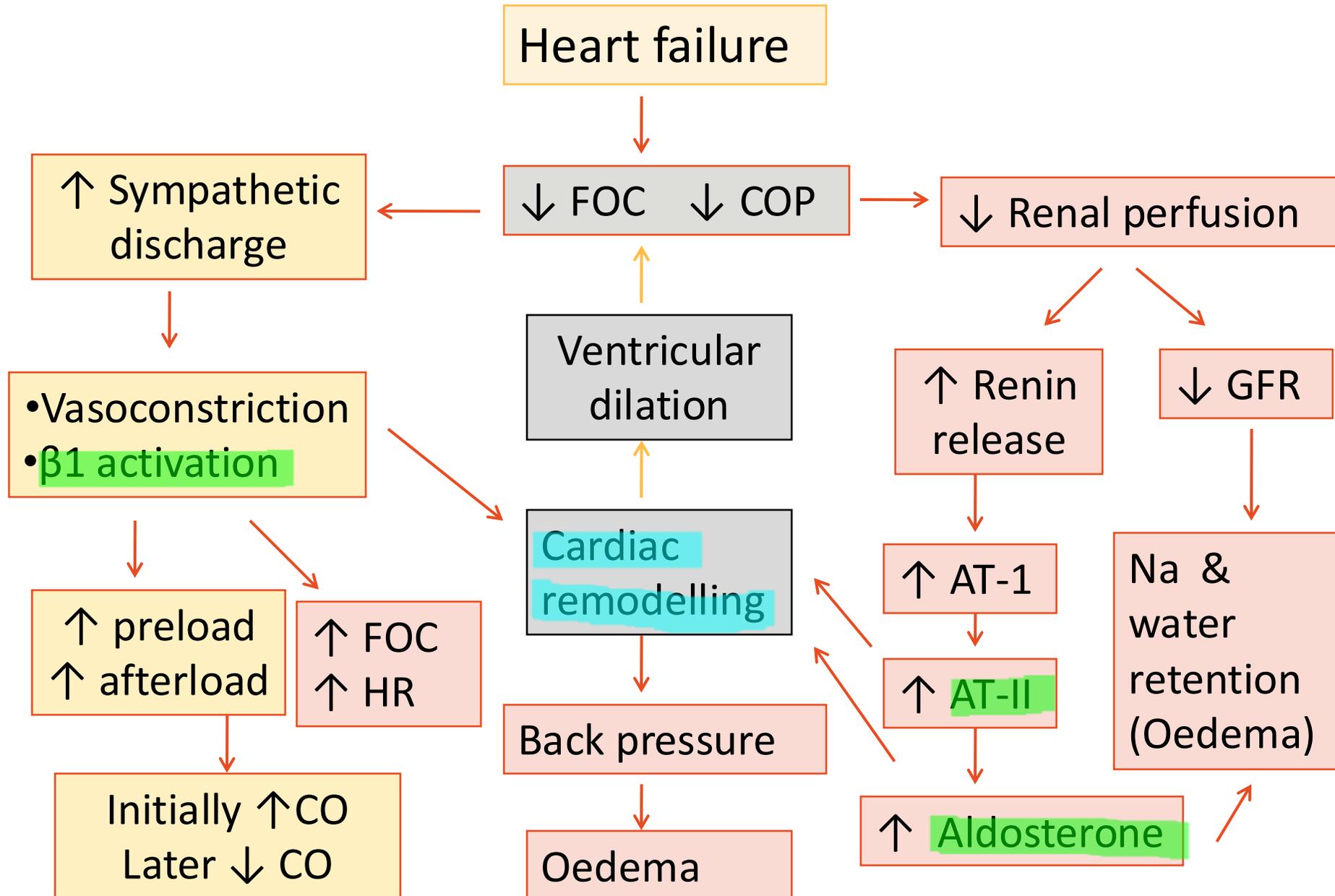
**Antiarrhythmic
agents**

Androgens

**Sodium-containing
preparations**

TNF-alpha inhibitors

Pathophysiology of heart failure

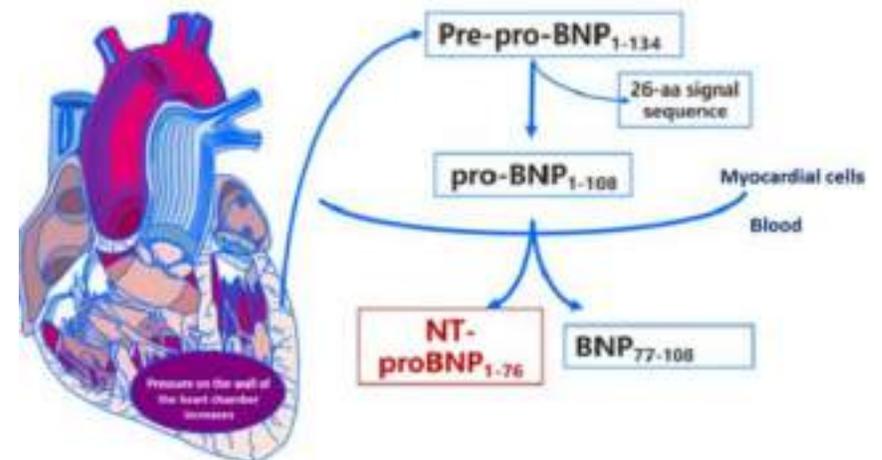


Atrial natriuretic peptides (ANP) & heart failure

- In heart failure, natriuretic peptides like **BNP and NT-proBNP** are released by the heart in response to **increased workload**, acting as a **diagnostic marker and a therapeutic target**
- **Importance:**
- **1- Diagnosis:** **Elevated BNP or NT-proBNP levels** in the blood are a key indicator of heart failure
- **2- Prognosis:** to predict the severity of heart failure and a patient's long-term risk. **High levels can indicate a higher risk of complications**
- **3- Monitoring treatment**

ANP

- **Brain natriuretic peptide (BNP)** and **N-terminal brain natriuretic peptide precursor (NT-proBNP)** belong to the natriuretic peptide (NP) family.
- The natriuretic peptide is a large family, the main members include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C natriuretic peptide (CNP), and so on.
- BNP and NT-proBNP are currently the **most important biomarkers for the diagnosis and treatment of heart failure.**
- **Therapeutic effects:**
 - Protective VD
 - Promotion of Na-water excretion
 - Reversal of remodeling



Diagnostic Criteria Of HF

- Triade of:

- **Symptoms:** shortness of breath, physical fatigue

- **Signs:** tachycardia, congested neck veins, pitting edema

- **Evidence of** structural or functional abnormality of heart, example: cardiomegaly

- Diagnosed by:

- Signs and/or symptoms caused by a structural and/or functional cardiac abnormality based on ECHO findings

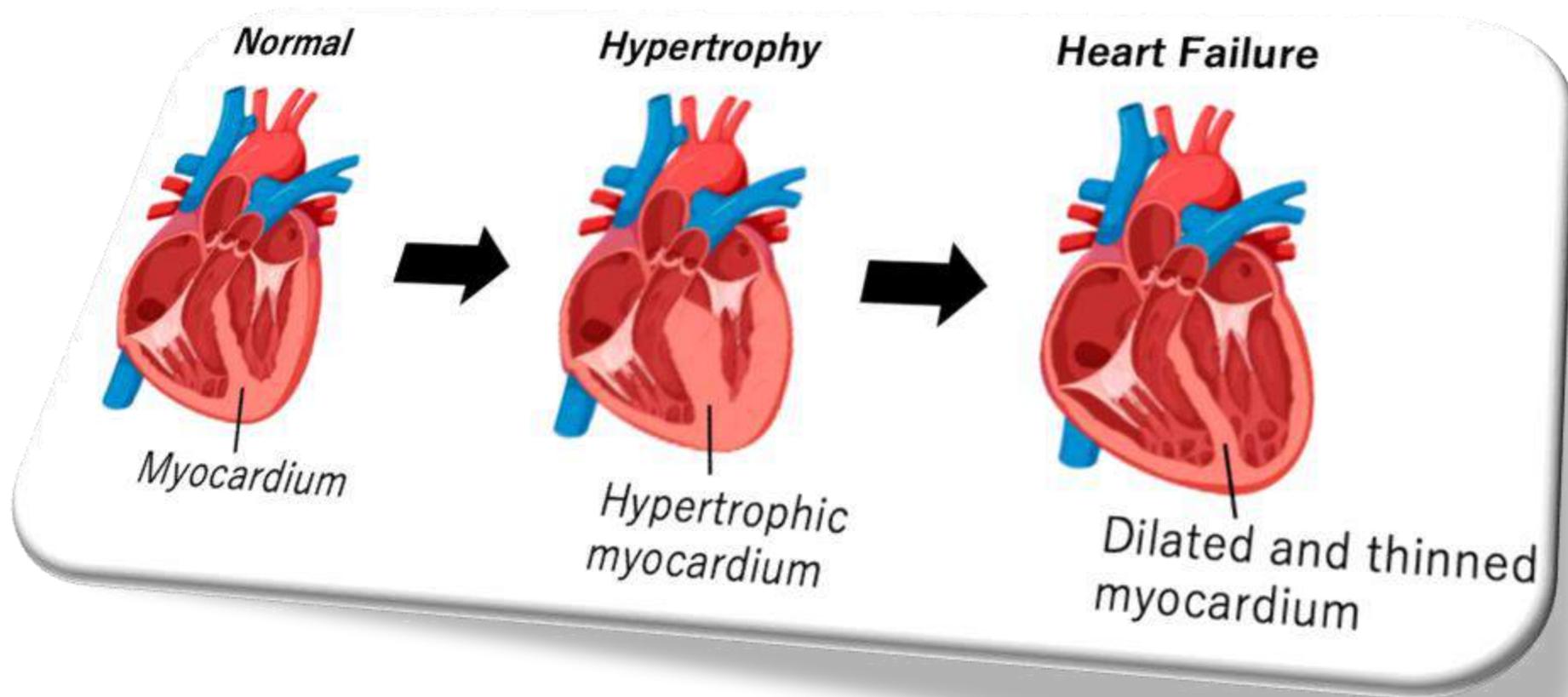
- Elevated natriuretic peptide levels (BNP or NT-proBNP*) OR objective evidence of cardiogenic, pulmonary or systemic congestion.



Factors Affecting Cardiac Output And Heart Failure

- Cardiac contractility
- Preload: volume overload: cardiac dilatation
- Afterload: tension overload: cardiac hypertrophy
- Heart rate: tachycardia

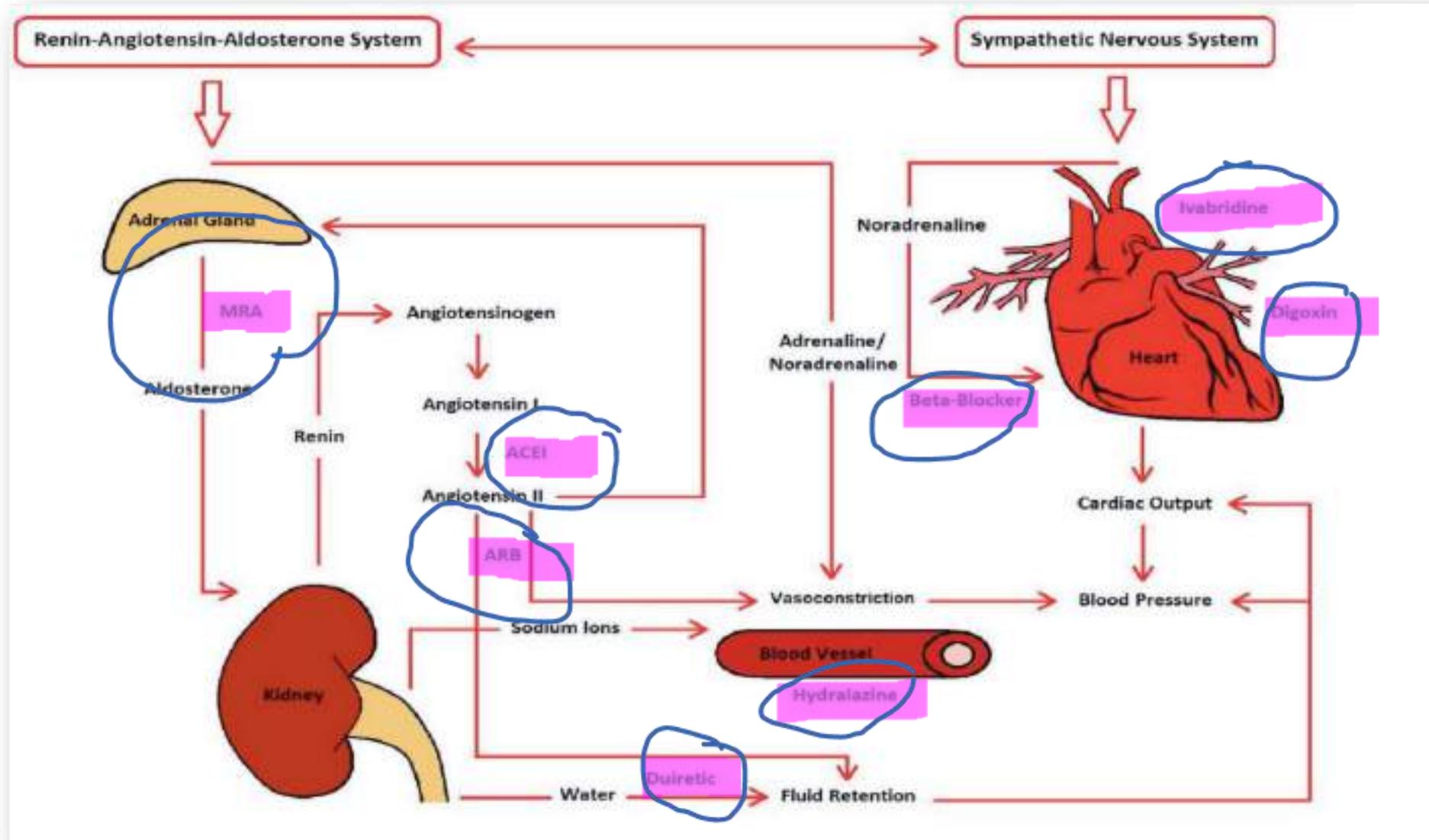
Cardiac changes in HF



Heart failure drugs



Drug therapy of congestive heart failure



Drugs used in HF

**Drugs that decrease
preload & afterload**

ACEIs & ARBs

**Drugs that decrease
preload**

**Duretics &
Venodilators**

**Drugs that decrease
after load**

Arteriodilators

**Drugs that decrease
heart rate**

**β - adrenoceptor
antagonists**

**Drugs increasing
cardiac contraction**

**Cardiac glycosides &
Phosphodiesterase
inhibitors**

Drug therapy of HF

•First line drugs for HF with reduced ejection fraction (HFrEF):

- ACEI (ARBs) or ARNI,
- Beta blockers (or ivabredine)
- MRA (mineralocorticoid receptor antagonist: aldosterone antagonist)
- SGLT2Is: Sodium-glucose cotransporter 2 (SGLT-2) inhibitors
- ± Positive inotropic drugs

•First line drugs for HF with volume overload (edema and congestion) :

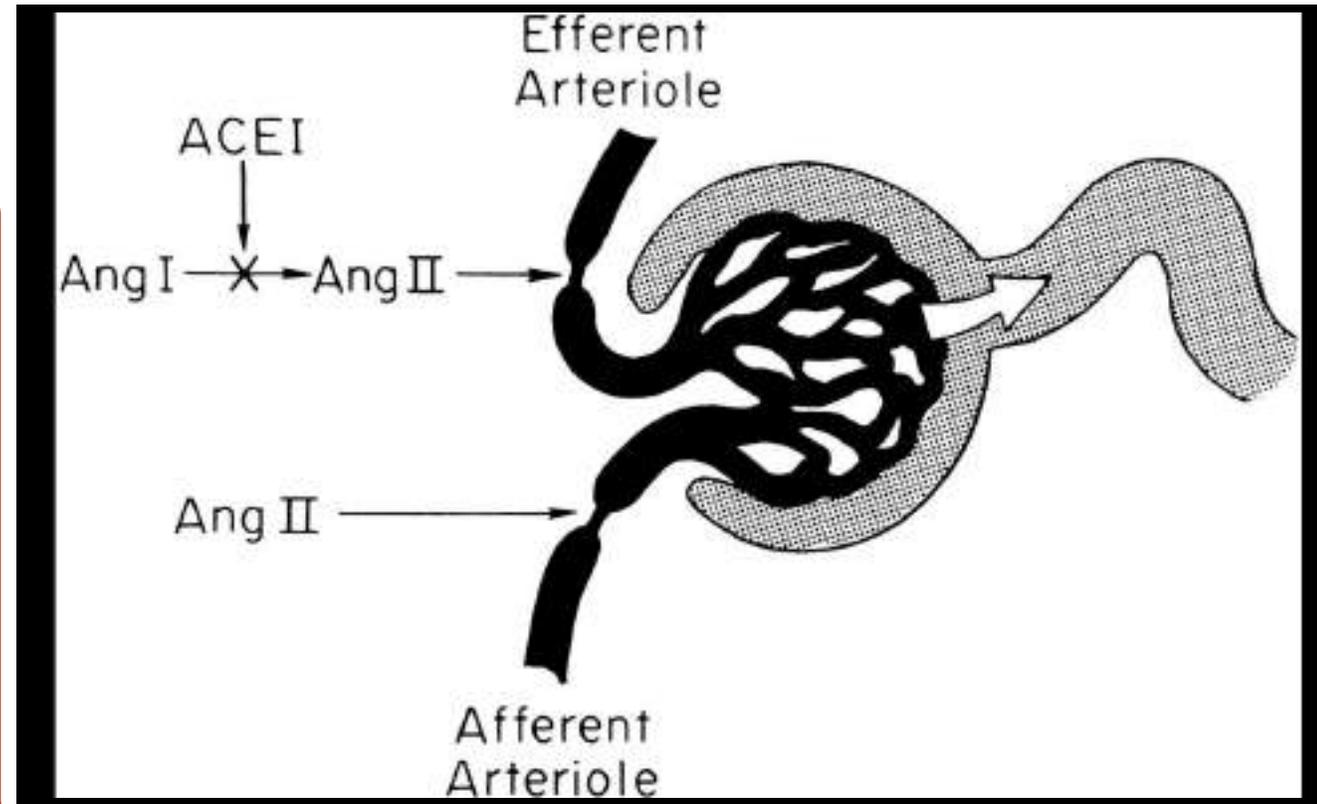
- Diuretics (symptomatic)
- ± Positive inotropic drugs

ACE Inhibitors & Angiotensin Receptor Blockers

- Along with digitalis and diuretics are now considered as first –line drugs for heart failure therapy
- ACEIs: Captopril, enalapril, ramipril, lisinopril
- AT1 receptor blockers: Losartan , candesartan, valsartan, telmisartan
- **Effects of converting enzyme inhibitors (ACEIs)**
 - ↓angiotensin II and aldosterone leading to (inhibition of RAAS):
 - 1- ↓Peripheral resistance (**Afterload**)
 - 2- ↓Venous return (**Preload**)
 - 3- ↓cardiac remodeling → ↓mortality rate
 - 4- ACE inhibitors are beneficial for many patients with renal impairment (and HF), as they can slow disease progression and reduce proteinuria.

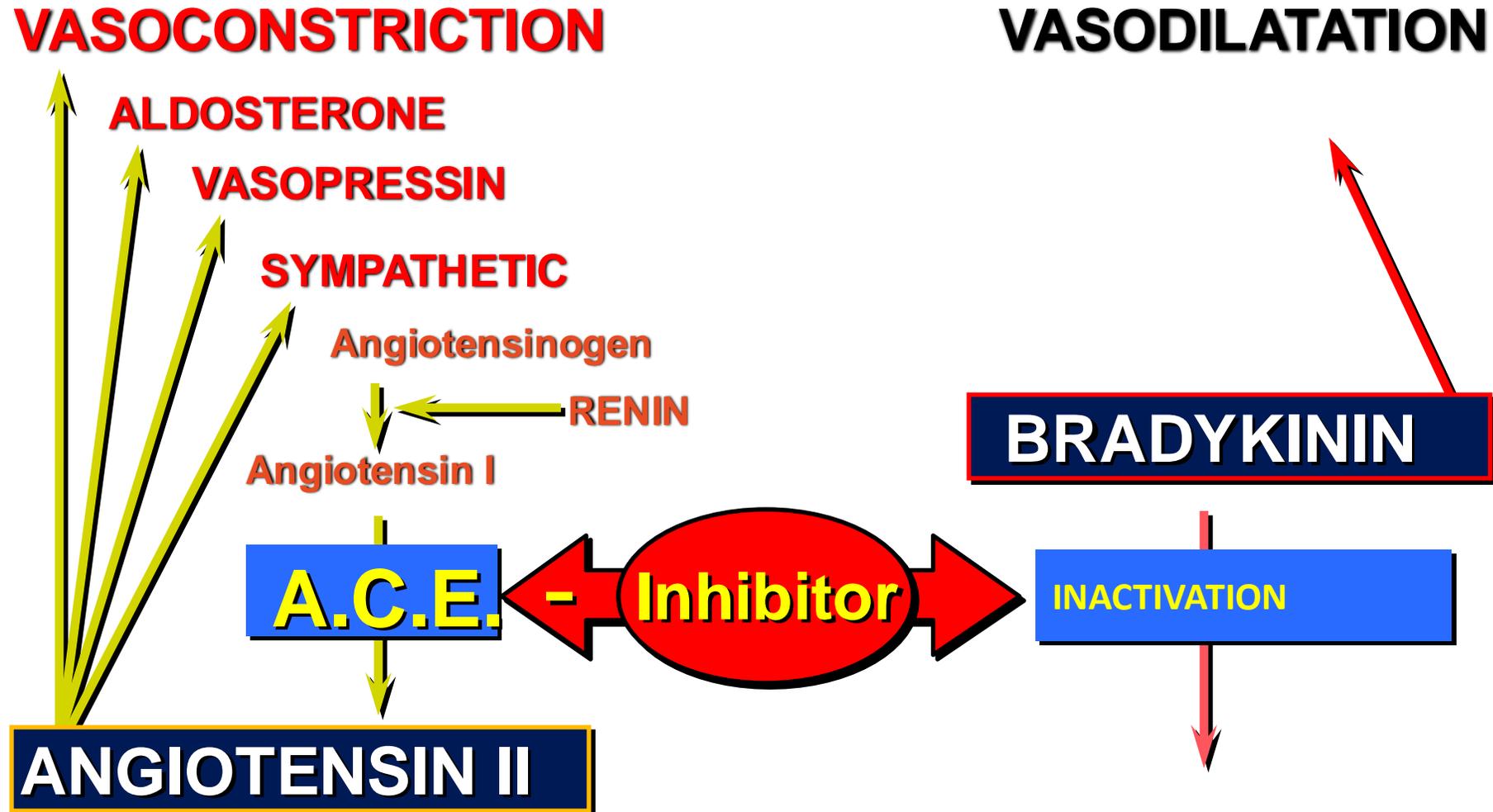
Effect of ACEIs on glomerular filtration

ACE inhibitors can cause acute renal failure in cases of renal artery stenosis (RAS) and should generally be avoided, especially in cases of bilateral or unilateral RAS affecting a single functioning kidney.

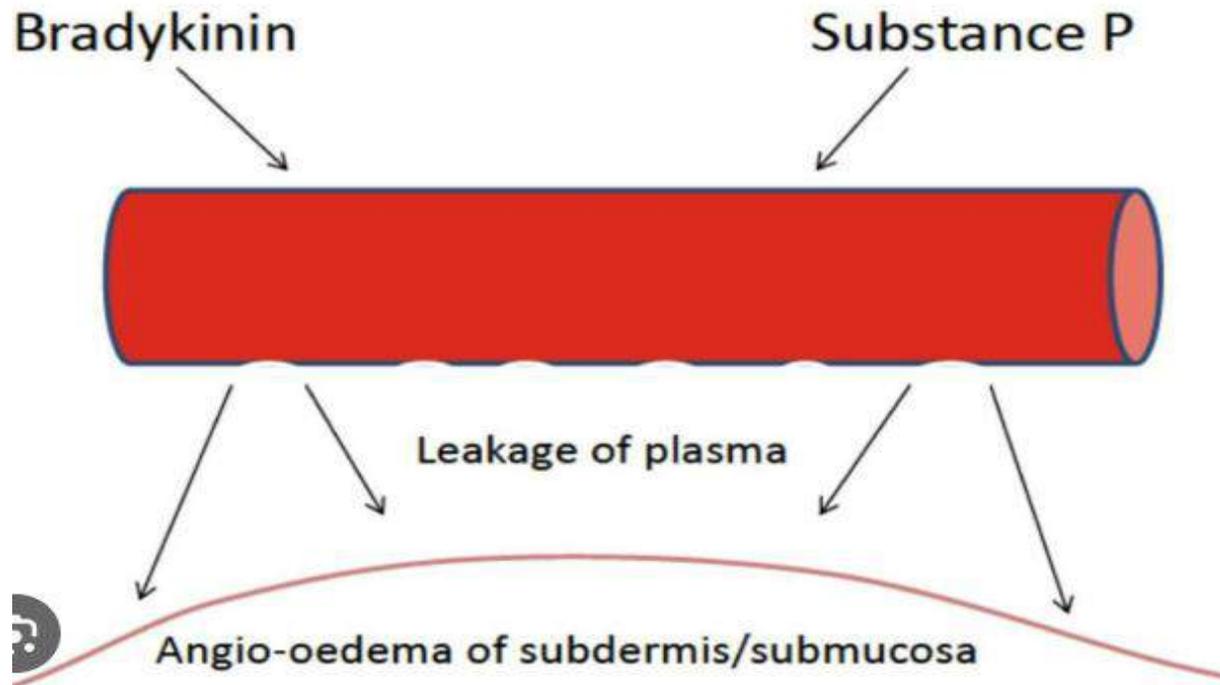


Angiotensin converting enzyme inhibitors

MECHANISM OF ACTION



Angioedema-induced ACEIs



Adverse effects of ACEIs

- 1- **T**eratogenic
- 2- **O**rthostatic hypotension
- 3- **P**otassium increase (hyperkalemia)
- 4- **C**ough (dry): 10%
- 5- **A**ngioedema: a potentially life-threatening side effect caused by an increase in bradykinin, which leads to swelling of deep tissues like the face, lips, tongue, and throat
- **Management:**
- **Immediate and permanent discontinuation** of the ACEI, with **alternative drugs** like angiotensin-receptor blockers (ARBs) sometimes used **with caution.**
- 6- **R**enal impairment: increase creatinine level
- 7- **D**izziness
- **Dry cough and angioedema are due to:**
- **elevated plasma bradykinins.**
- **ARBs:** less effective and typically used **in patients who can not tolerate ACEIs.**
- **ACEIs and ARBs are similar in side effects, but dry cough and angioedema are less noted in ARBs**

Top card

B-Blockers In Heart Failure

• Benefits in HF:

- Reduce catecholamine myocyte toxicity (**remodeling**)
- Inhibit renin release
- Increases beta receptor sensitivity (up regulation).
- Decrease heart rate
- Decrease mortality rate 34%: improved long-term survival and fewer hospitalizations

• Adverse effects:

- 1- Hypotension 2- Rare but severe: bradycardia, A-V block

• Contraindications in HF:

- 1- Beta blockers in large dose
- 2- Acute HF

• Beta blockers approved in HF (stable cases, in small doses):

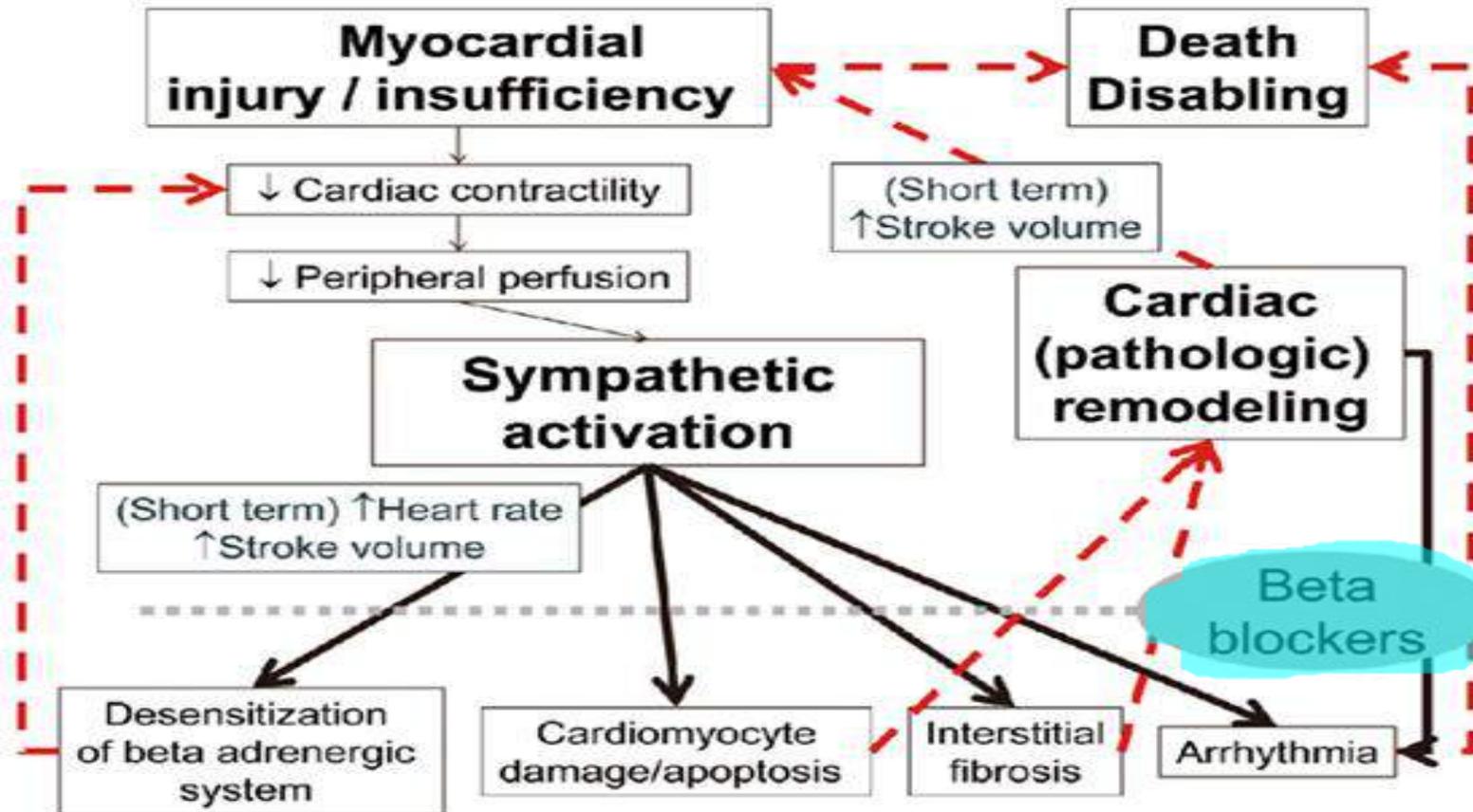
1- Bisoprolol

2- Metoprolol 3- Carvedilol (additional VD)

B blockers in HF

- **Worsening symptoms or signs** (e.g. increasing dyspnoea, fatigue, oedema, weight gain):
 - **Increase dose of diuretic** or **halve dose of beta-blocker**
 - Review patient in 1–2 weeks
 - **If serious deterioration**, **halve** dose of beta-blocker or **stop** this treatment (rarely necessary)
- **Contraindications:**
 - Total AV block
 - Severe poorly controlled asthma
 - Critical limb ischaemia

Effects of B-blockers in HF



Diuretics

- Among First-line therapy of heart failure (cornerstone of heart failure management)
- Role in HF:
 - 1- Remove the signs and symptoms of volume overload (pulmonary congestion/ peripheral edema).
 - 2- Reduce salt and water retention (Natriuresis) → ↓ventricular preload and venous pressure.
 - 3- Reduction of cardiac size → improve cardiac performance
- **Loop diuretics – furosemide:** most powerful and used for most patients
- **Thiazide Diuretics- less effective but indicated in patients with hypertension and mild fluid retention** chlorthiazide, hydrochlorthiazide
- **Side effects of diuretics:** metabolic alkalosis, electrolyte imbalance (hypokalemia) and hypovolemia
- **N.B. Diuretics do not improve the mortality rate in patients**

K⁺ Sparing Diuretics (aldosterone antagonists: MRA: Mineralocorticoid receptor antagonists)

- **Spironolactone, triamterene, amiloride, eplerenone:**

- are weak diuretics-for achieving volume reduction with minimal K⁺ loss

- **Advantages of spironolactone:**

- 1- **Preserve potassium ion:** prevents hypokalemia

- 2- **Decreases mortality** in cases of severe HF

- 3- **Reverse aldosterone-induced remodeling**

- **Dose:** one tablet lasilactone (furosemide and spironolactone) 50 mg in the morning 5 days a week.

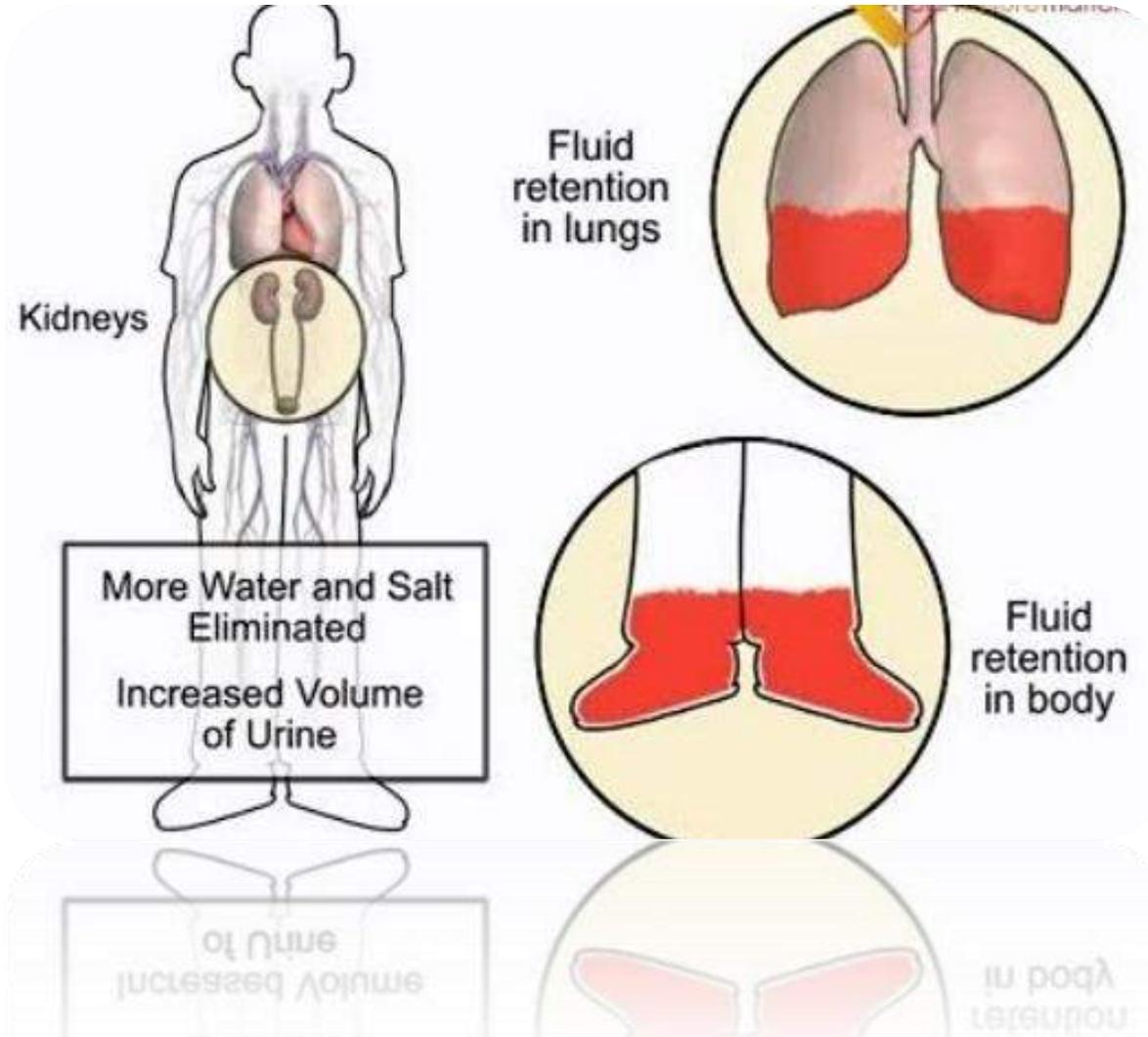
- **Side effects: gynecomastia:**

- **In males: breast tenderness and breast enlargement**

- **This is due to its anti-androgen effects**

- **A more selective mineralocorticoid receptor antagonist like eplerenone can be an alternative to minimize this risk.**

Diuretics in HF



Vasodilators

- Indications of vasodilators in HF:

- **patients intolerant to ACEIs, ARBs**

- Arterioldilators: hydralazine , minoxidil, nicorandil

- **Hydralazine:**

- Direct acting vasodilator

- Reduces both right and left ventricular afterload by reducing pulmonary and systemic vascular resistance

- Results in increased cardiac output

- Reduces renal vascular resistance and increases renal blood flow

- **Increases renal blood flow more than any other vasodilator except ACE inhibitors**

- Indications:

- **Preferred drug in CHF (ACE intolerant) with renal impairment**

- **Combined with nitrates to overcome nitrate tolerance**

- **Black people with advanced HF**

- **Intolerance to ACEIs and ARBs**

Venodilators: nitrates

•How nitrates are helpful in CHF?

- Reduce preload

- Coronary artery dilatation- reperfusion (by generation of NO: vasodilatation)

•If given alone their efficacy is limited due to:

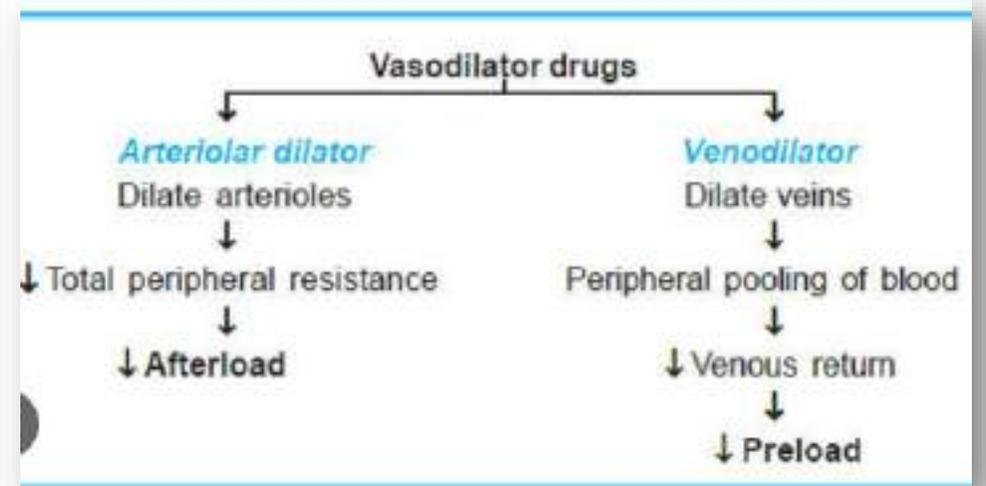
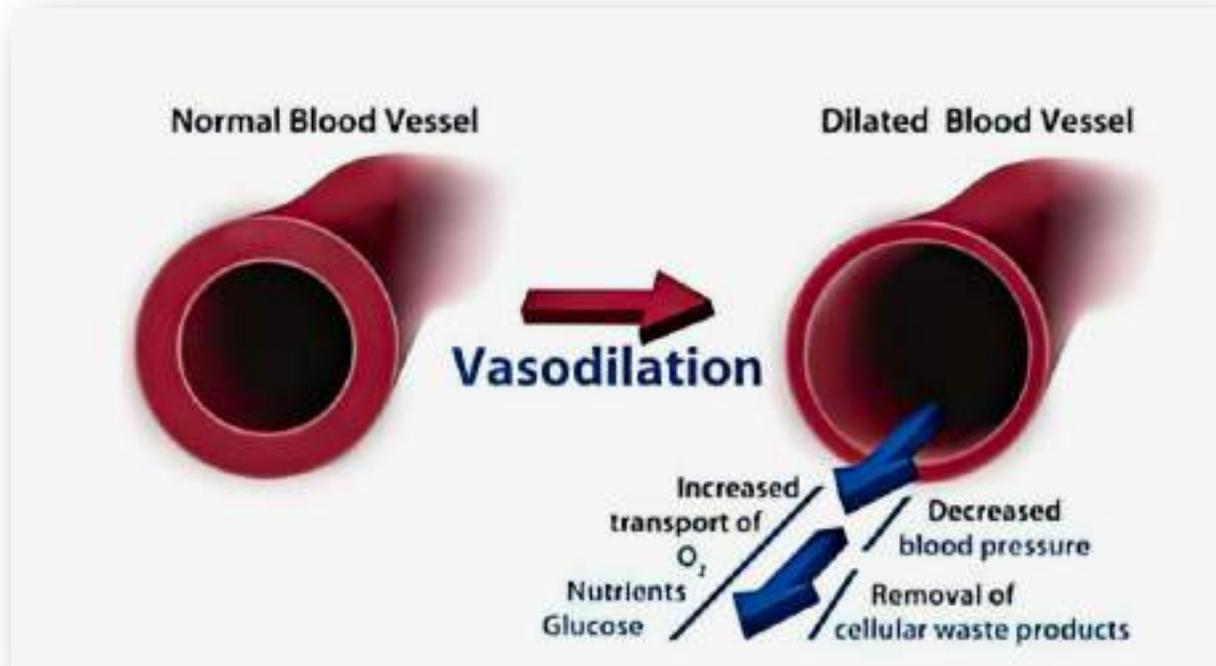
- ✓ limited effect on systemic resistance

- ✓ Nitrate tolerance

•Often combined with other vasodilators for better results:

- **Hydralazine/isosorbide dinitrate(Bidil)** is a fixed-dose combination: improve mortality in some cases of HF.

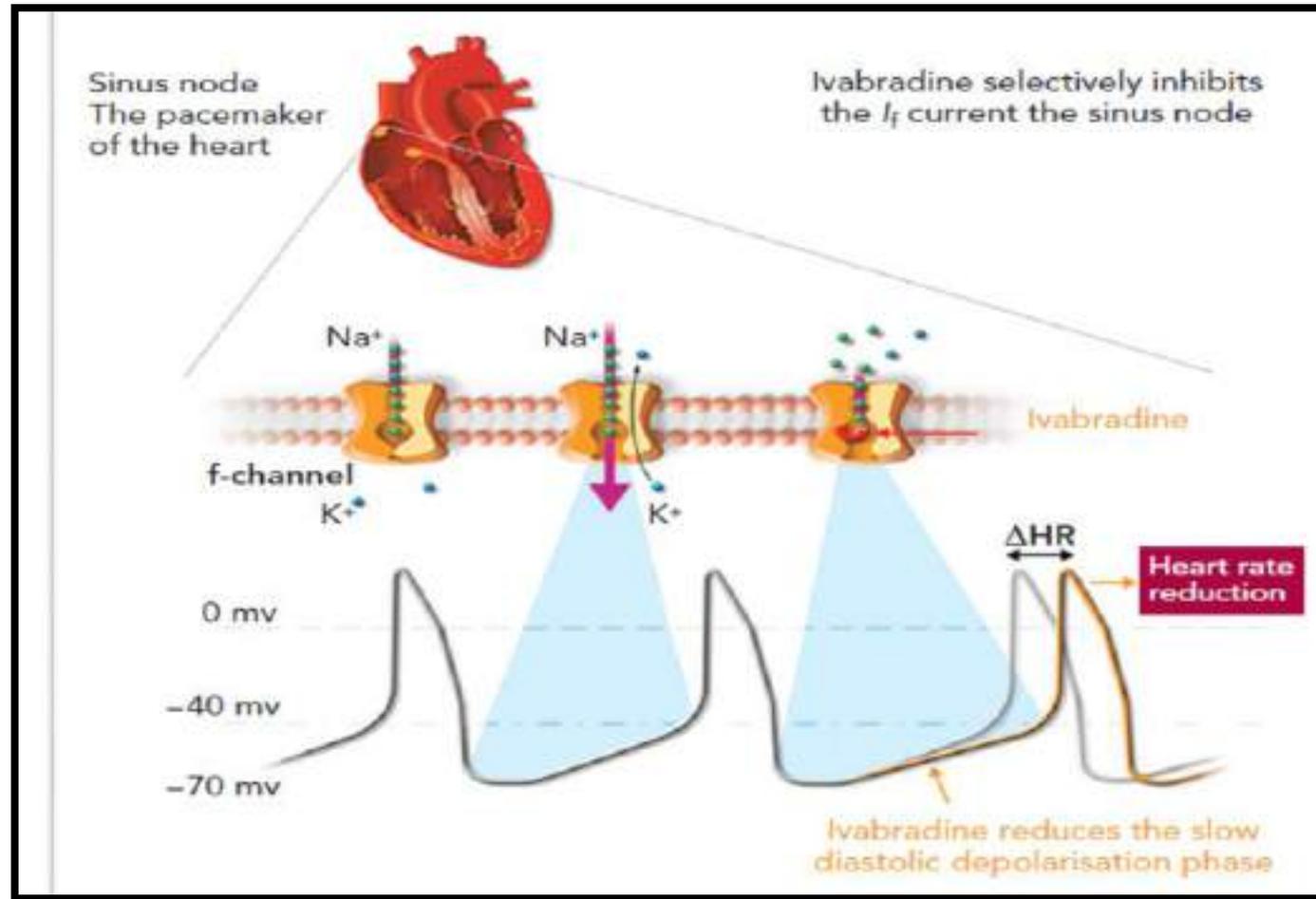
Effects of vasodilators in HF



Ivabredine

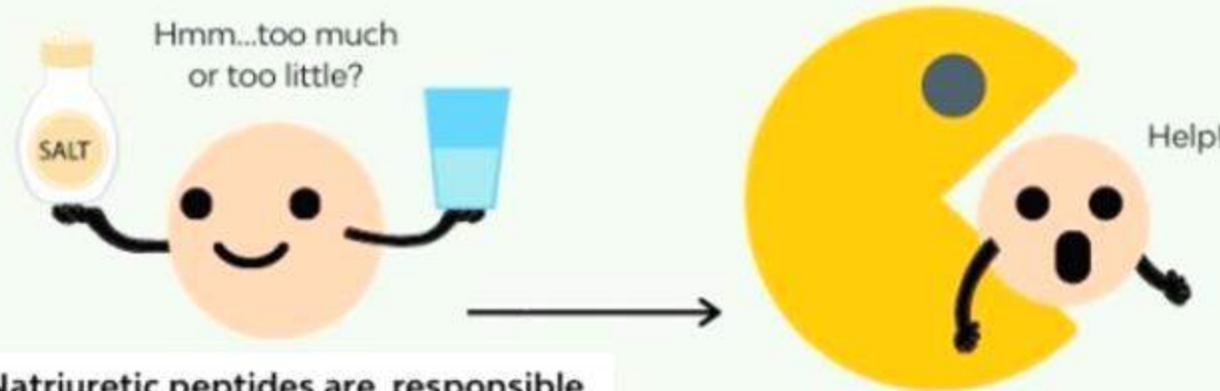
- **The First Selective and Specific I_f Inhibitor**
- Blocks the channel responsible for the cardiac pacemaker spontaneous firing (funny channel), $I(f)$, which regulates heart rate.
- Without affecting any other cardiac ionic channels (including calcium or potassium).
- **This results in reduced heart rate.**
- **Indications:**
- patients of CHF not responding or intolerant to B blockers
- **Adverse effects:**
- Bradycardia
- Atrial fibrillation
- Phosphenes (vision disorder).

Mechanism of action of ivabradine



ARNI (angiotensin receptor blocker/neprilysin inhibitor) (Entresto)

SACUBITRIL/VALSARTAN MECHANISM OF ACTION



Natriuretic peptides are responsible for salt and water balance in the body

Neprilysin is an enzyme that breaks down natriuretic peptides, preventing them from doing their job

Angiotensin II is a hormone that causes vasoconstriction and increases aldosterone secretion leading to high blood pressures



- Sacubitril inhibits neprilysin enzymes
- Valsartan blocks angiotensin II receptors

ARNI

- **Adverse effects of Sacubitril-valsartan:**

- Hypotension
- Hyperkalemia
- Renal failure

- **Indications:**

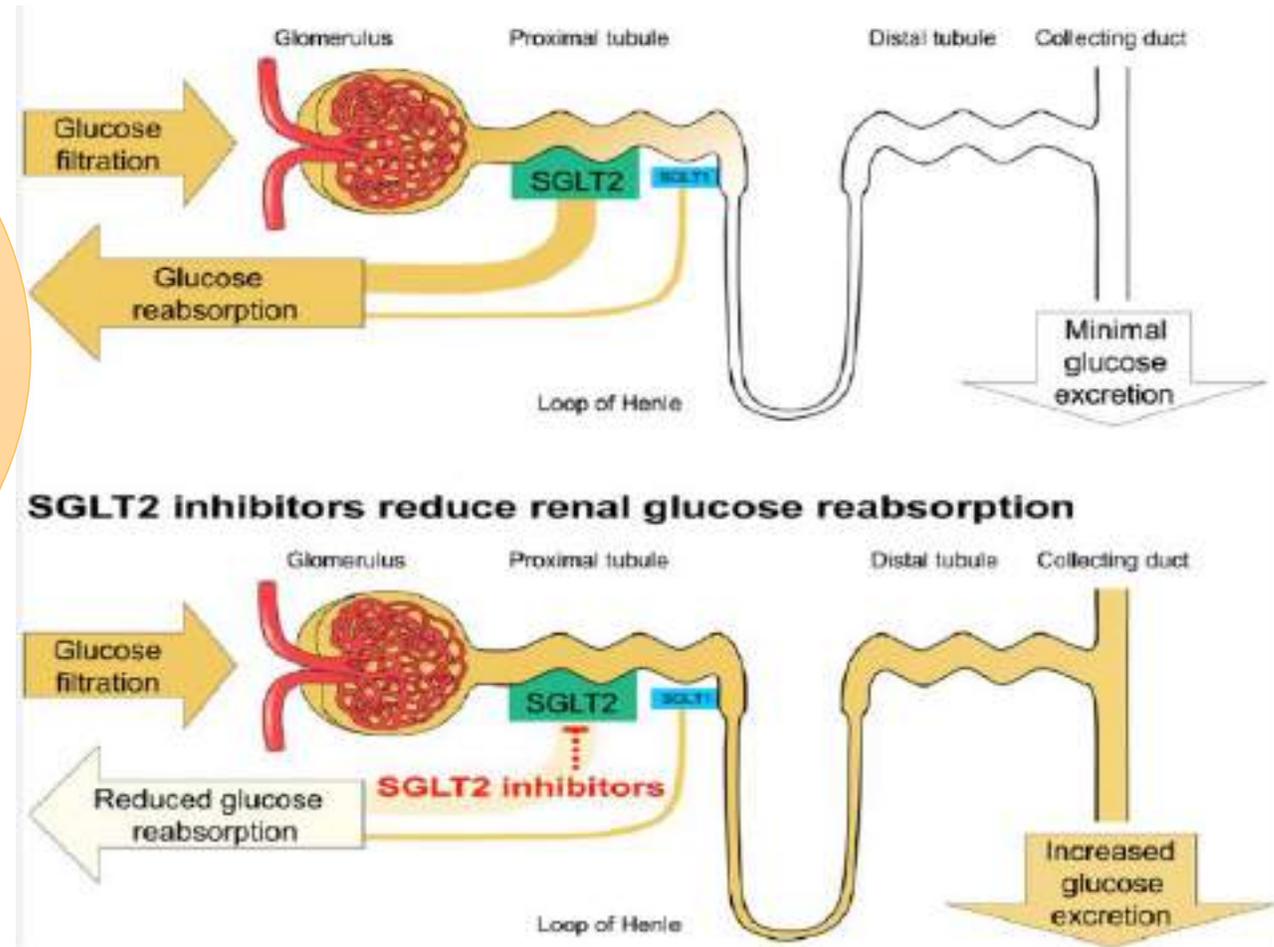
- ARNI new class of drugs indicated in **patients not responding to ACEIs or B blockers**

SGLT2 inhibitors (gliflozines)

- **Gliflozines** are a class of drugs, also called **SGLT2 inhibitors** for treatment of type 2 diabetes **by increasing the excretion of glucose in the urine.**
- They are also used for treatment of heart failure and chronic kidney disease due to their **benefits:**
- **1- Improved cardiovascular outcomes:** reduce the risk of cardiovascular events and hospitalizations
- **2- Reduced kidney workload**
- **3- Unique osmotic diuretic effect.**
- **4- Reduction in sympathetic nervous system activity**
- **5- Reduced oxygen consumption by the kidneys.**

SGLT2 inhibitors

sodium-glucose cotransporter-2 (SGLT2): protein in the **proximal convoluted tubules** of the kidneys, which are responsible for reabsorbing about 90% of the filtered glucose



SGLT2 inhibitors (gliflozines)

- **Examples:**

- Dapagliflozin
- Empagliflozin

- **Side effects:**

- **1- Genitourinary fungal infections** (due to the increased glucose in the urine)
- **2- Ketoacidosis**: A rare but serious condition.

Drugs That Increase Contractility
positive inotropic drugs

Inotropic Drugs

- **Cardiac glycosides:**

- Digoxin, digitoxin

- **Phosphodiesterase inhibitors:**

- Amrinone , milrinone

Inotropic Drugs

Cardiac glycosides: Digoxin



William Withering
1785



Foxglove plant

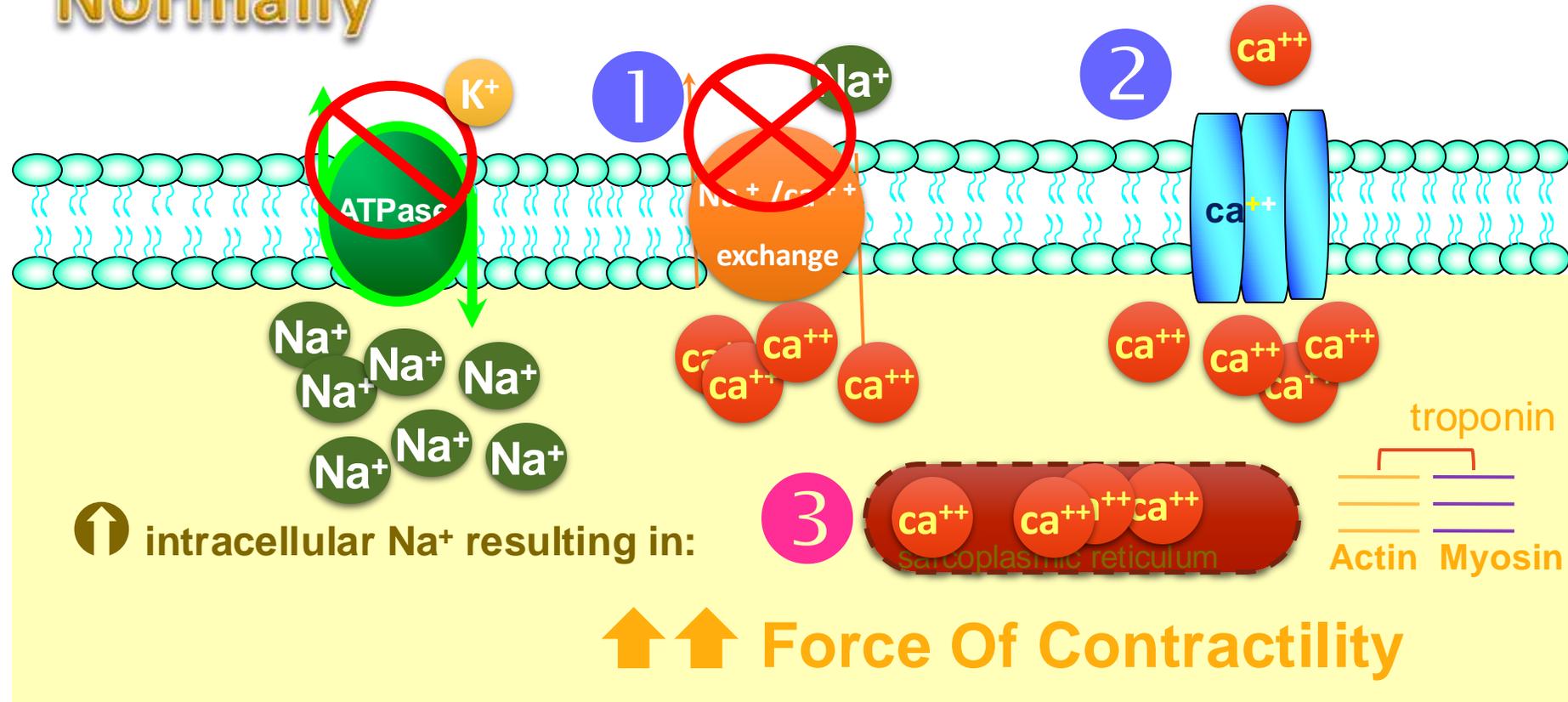
Beneficial Effects Of Digoxin In HF

- (Increasing the contractile force of the cardiac muscles)
- This effect is manifested in patients with heart failure, this results in:
 - 1- Increased C.O.P: **increasing renal blood flow**
 - (inhibition of RAAS): decreasing systemic & pulmonary congestion
 - Diuresis: relief of edema
 - Inhibition of central sympathetic stimulation:** normalization of BP
 - Improving tissue hypoxia**
 - 2- Bradycardia: diminishing tachycardia: increasing filling time:  COP
 - 3- Decreased heart size

Mechanism Of Action Of Digitalis

Digitalis concentrated in myocardium 15 folds more than in other tissues

Digitalis
Normally

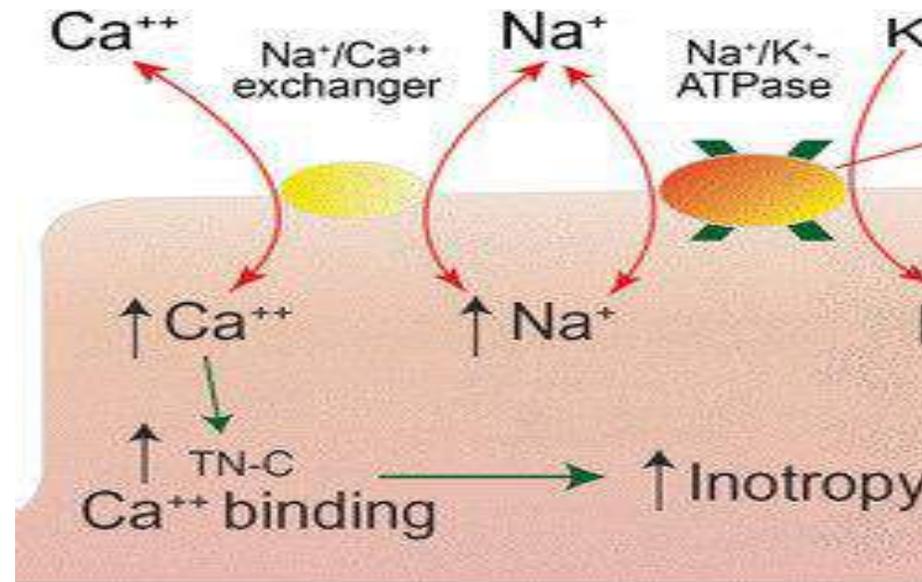


Digitalis Mechanism Of Action

- **Digitalis increase intracellular free Ca^{+2} in CARDIAC CELL**, during systole .
- **Ca^{+2} inhibits troponin (relaxing protein):**
- Facilitates excitation -contraction coupling between actin and myosin leading to increased cardiac contractility.
- **N.B.** Digitalis inhibit $\text{Na}^{+}/\text{K}^{+}$ ATPase by competition **with K^{+}** , So **hypokalemia increase Digitalis toxicity** , while K^{+} administration improve toxicity of digitalis.
- In therapeutic dose leads to **partial inhibition** of $\text{Na}^{+}/\text{K}^{+}$ ATPase enzyme

Digitalis increase intracellular free Ca^{+2} in cardiac cells by :

- 1- Inhibition of membrane bound $\text{Na}^+ \text{K}^+ \text{Atpase}$ enzyme: \uparrow increasing intracellular Na^+ \longrightarrow \uparrow increasing free intracellular Ca^{+2}
- 2- Digitalis may directly facilitate the entry of Ca^{+2} into cardiac cells during the plateau of the action potential.
- 3- Digitalis may increase the release of stored Ca^{+2} from the sarcoplasmic reticulum.



Pharmacological actions

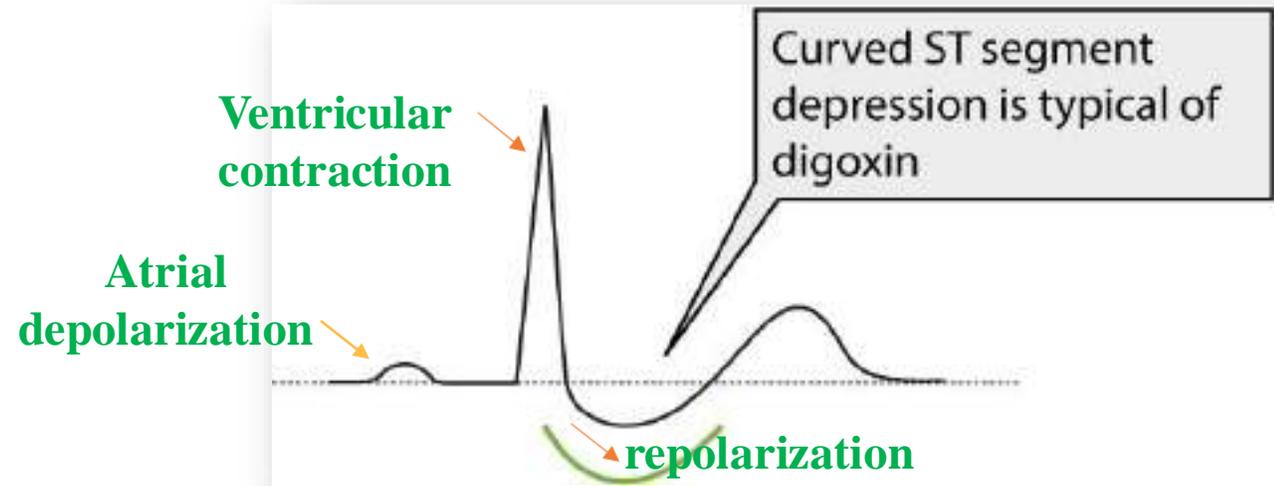
Cardiac

- **Contractility**: ↑force of contraction & Cardiac Output: +ve inotropic
- **Heart rate**: - ve chronotropic: vagal stimulation: by direct and indirect mechanisms
- **Conductivity**: - ve dromotropic ↓ CV in AV node
- **Increased automaticity**: ectopic foci
- **Increased excitability**: arrhythmia
- **Rhythmicity**: disturbed

Extra cardiac

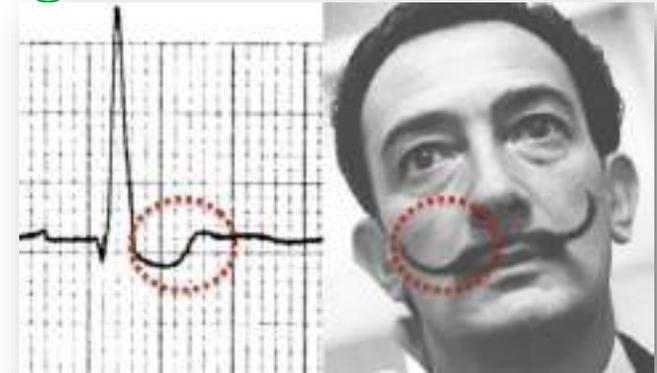
- **Kidney**:
 - Improvement in circulation and renal perfusion
 - Retained salt and water is gradually excreted
- **CNS**:
 - Nausea, vomiting

Digitalis effects on ECG



• ECG

- 1- Prolongation of P-R interval
- 2- High R wave
- 3- Depressed S-T segment: **scooped ST segment**: "Salvador Dali" sign
- 4- Inverted T- wave
- 5- Bradycardia
- 6- Any type of arrhythmia: pulsus bigemini or trigemini



Clinical Uses Of Digoxin

•1- Congestive heart failure: **mild to moderated cases of HFrEF (less than 40%) who do not respond to other medications.**

•2-CHF associated with Cardiac arrhythmias:

- Atrial fibrillation
- Atrial flutter
- Paroxysmal supraventricular tachycardia

•**DOSE:** Lanoxin tablet 0.25 mg once in the morning after breakfast 5 days/ week

•**Sever HF:**

•**Loading dose: 2 tab. Twice daily for 2 days or 2 tab, thrice daily for 1 day**

•**Then maintenance dose**



Contraindications

Absolute

- 1- Heart block
- 2- WPW syndrome
- 3- Hypertrophic obstructive cardiomyopathy
- 4- Ventricular arrhythmia

Relative

- 1- Bradycardia: beta blockers, verapamil, myxedema, sick sinus syndrome.
- 2- Systemic or pulmonary hypertension
- 3- Renal and hepatic impairment
- 4- DC cardioversion
- 5- MI
- 6- Acute myocarditis of rheumatic fever

Drug interactions of digitalis

- **1- Antacids, cholestyramine:** decrease digitalis absorption
- **2- Atropine:** increases digitalis absorption while metoclopramide decrease
- **3- Quinidine:** decreases digitalis clearance
- **4- K- losing diuretics:** increase digitalis toxicity

Toxicity of digoxin

Extra-Cardiac

- **GIT:** Nausea & vomiting, anorexia
(**first to appear**)
- **CNS:** convulsions
- **Vision:** visual disturbances: halos, scotoma, sudden loss of vision, yellow vision
- **Endocrine:**
Gynaecomastia



Cardiac

- **Bradycardia**
(first cardiac toxic sign)
- **Pulsus bigemini**
- **Atrial flutter** → fibrillation
- **Ventricular extra-systole** → tachycardia → fibrillation
- **Partial heart block** → complete block

Factors Increasing Digitalis Toxicity

- Small (Lean) body mass
- Old age
- Renal diseases
- Hypokalemia
- Hypercalemia
- Drug interactions:
 - **Diuretics** → hypokalemia (arrhythmia)
 - **Quinidine** : ↑ plasma level of digitalis

Treatment Of Digitalis Toxicity

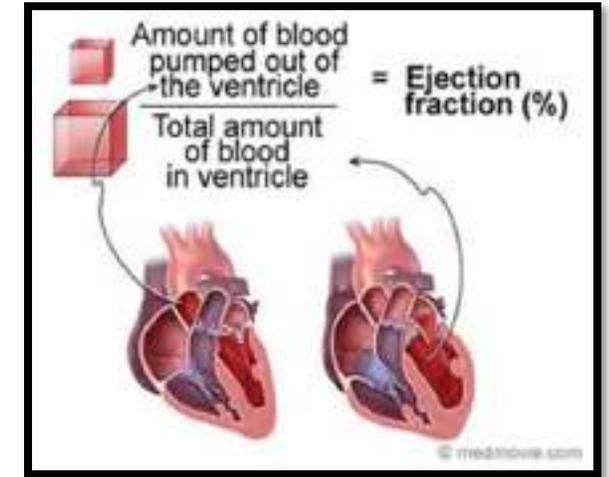
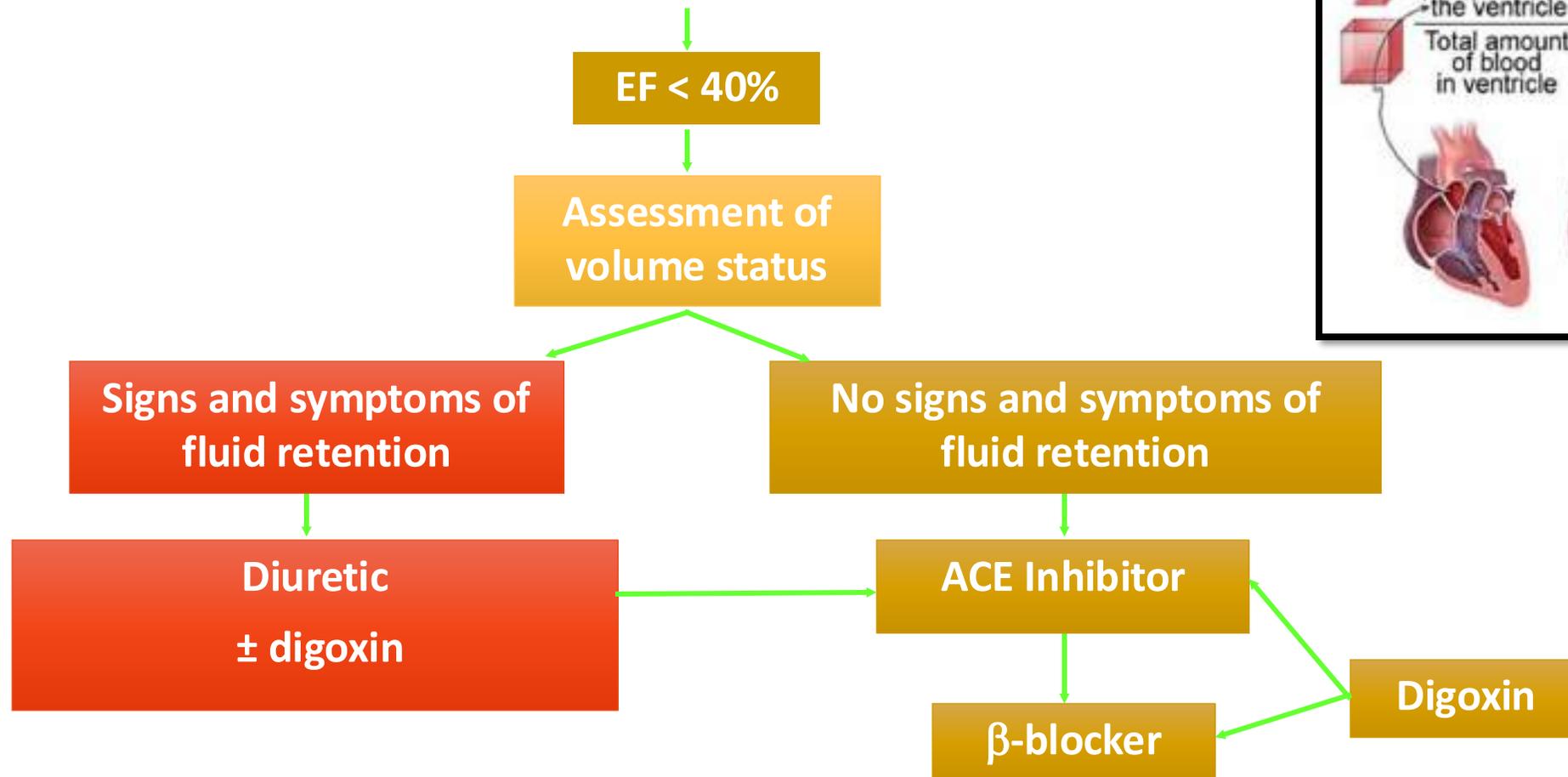
- 1- Stop digitalis
- 2- Oral or parenteral potassium supplements
- 3- For ventricular arrhythmias:
 - Lidocaine IV drug of choice
- 4- For supraventricular arrhythmia:
 - Propranolol may be given IV or orally
- 5- For AV block and bradycardia
 - Atropine IM
- 6- Digoxin antibodies (antidigoxin antibodies) (IgG): (digibind) FAB fragment
life saving: most specific

Management Of Chronic Heart Failure

- Lifestyle changes
- Drug therapy
- Surgery for correctable problems
- Implantable devices
- Heart transplant
- **Diet and lifestyle measures**
- Moderate **physical activity**, when symptoms are mild or moderate; or bed rest when symptoms are severe.
- **Weight reduction**
- **Sodium restriction** – excessive sodium intake may precipitate or exacerbate heart failure, thus a "no added salt" diet (60–100 mmol total daily intake) is recommended for patients with CHF.
- **Stop smoking**

Approach to the Patient with HFrEF

Assessment of LV function (echocardiogram)



References

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Thank you 