Drug therapy of congestive heart failure

Dr. Nashwa Aborayah
Associate professor of clinical and experimental pharmacology
Mu'tah University- Faculty of Medicine
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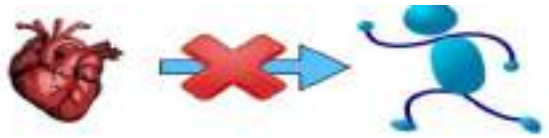
Objectives

- 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 inspite of good venous retur**



- 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 = SV/EDV):

Systolic HF: HFrEF

Diastolic HF: HFpEF

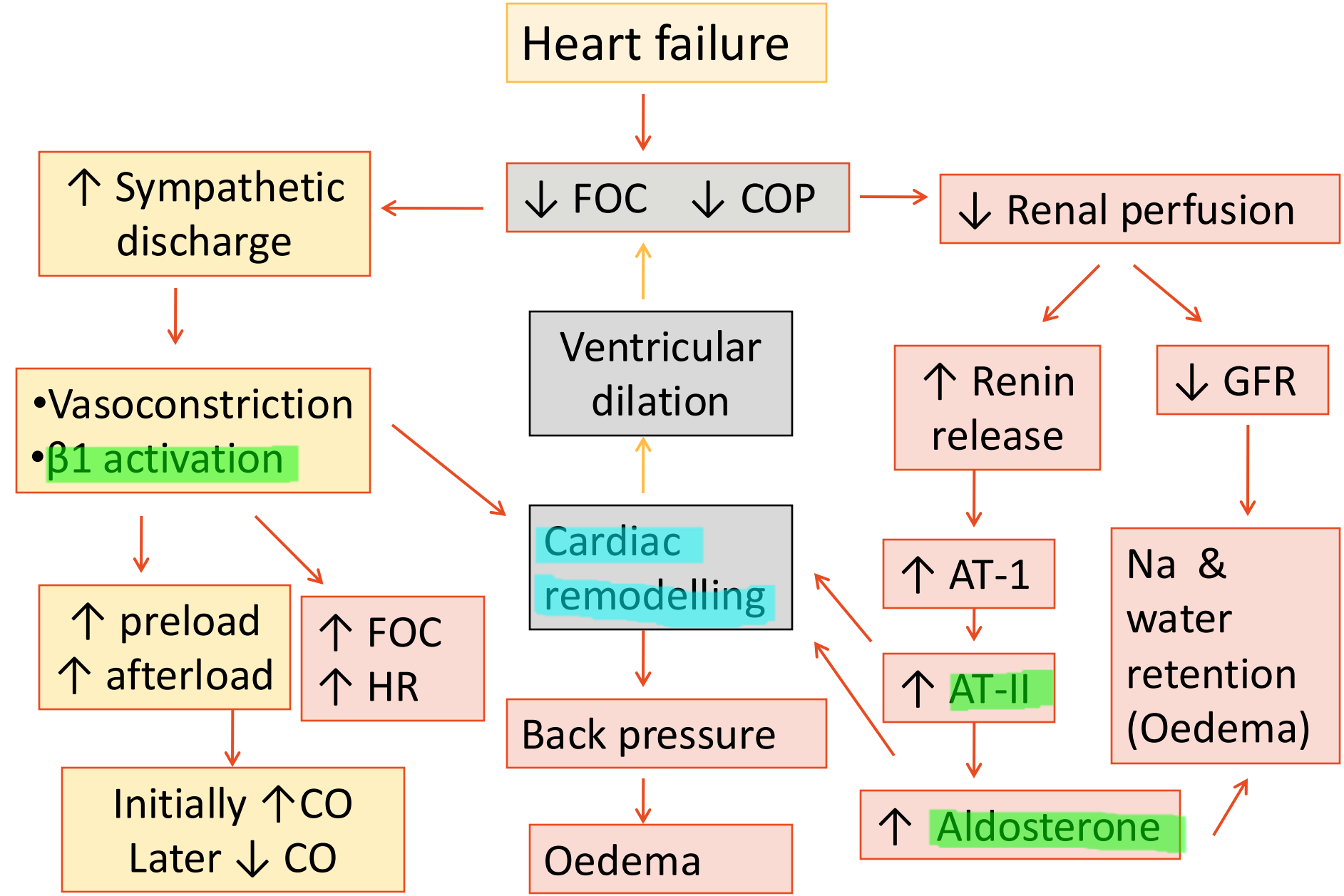
Causes of HF (classification)

Etiology	Left-sided HF	Right-sised HF
Increased preload	AR, MR, VSD, hyperdynamic circulation	TR, PR, VSD, hyperdynamic circulation
Increased afterload	AS, Aortic cortication, 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

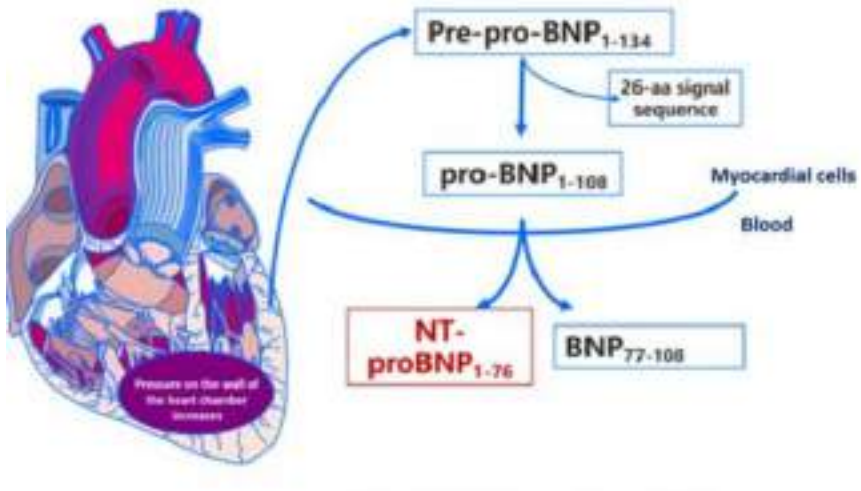


Atrial natriuretic peptides (ANP) & heart failure

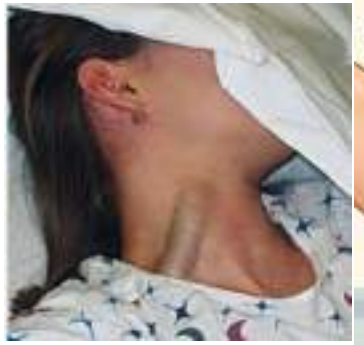
- In heart failure, **natriuretic peptides** like **BNP and NT-proBNP** are released by the heart in response to **increased workload**, acting as a **diagnostic marker and a therapeutic target**
- **Importance:**
- **1- Diagnosis**: **Elevated BNP or NT-proBNP levels** in the blood are a key indicator 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 remolding



Diagnostic Criteria Of HF

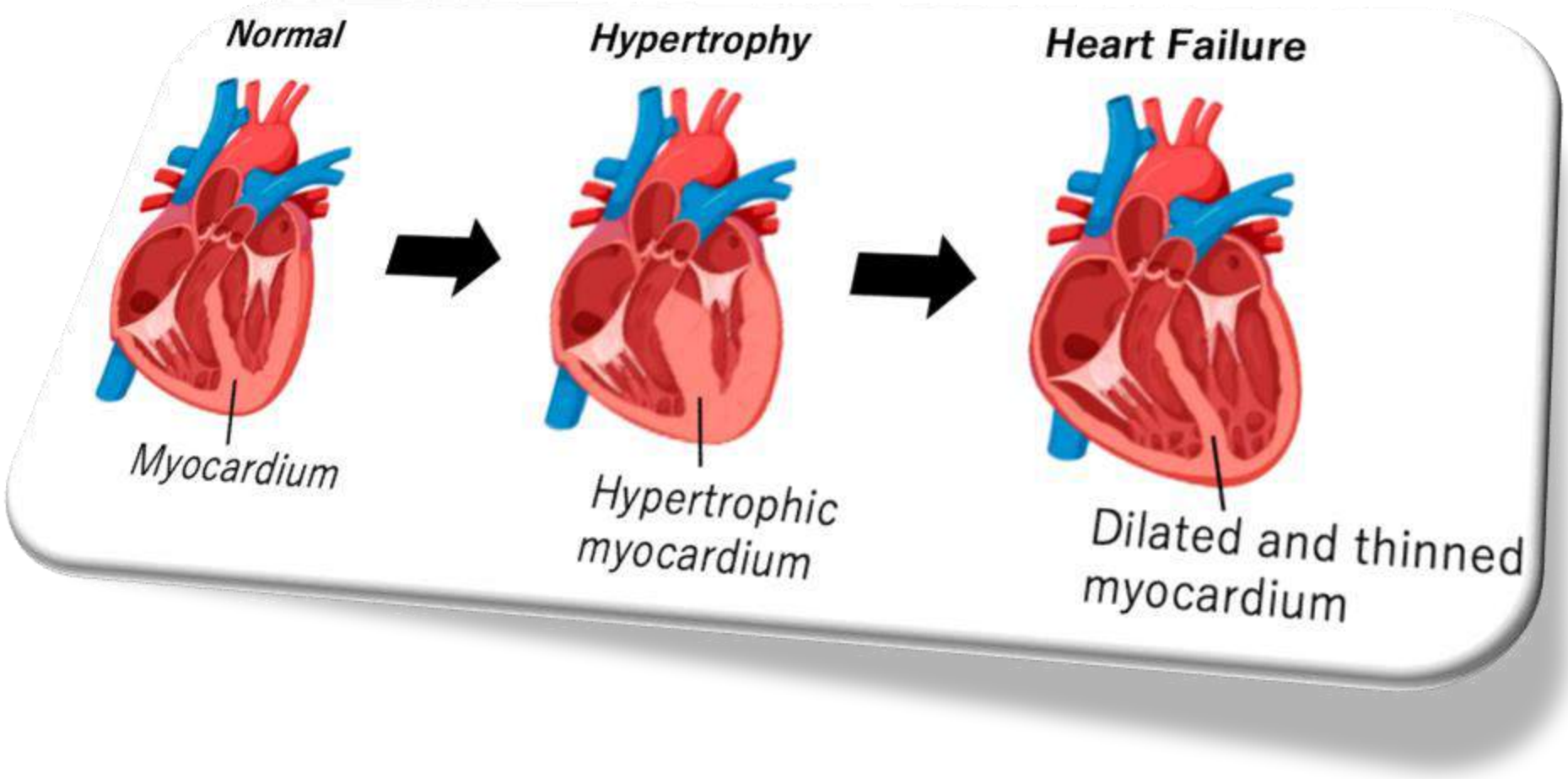


- **Triade of:**
- **Symptoms: shortness of breath, physical fatigue**
- **Signs: tachycardia, congested neck veins, pitting edema**
- **Evidence of structural or functional abnormality of heart, example: cardiomegaly**
- **Diagnosed by:**
- **Signs and/or symptoms caused by a structural and/or functional 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

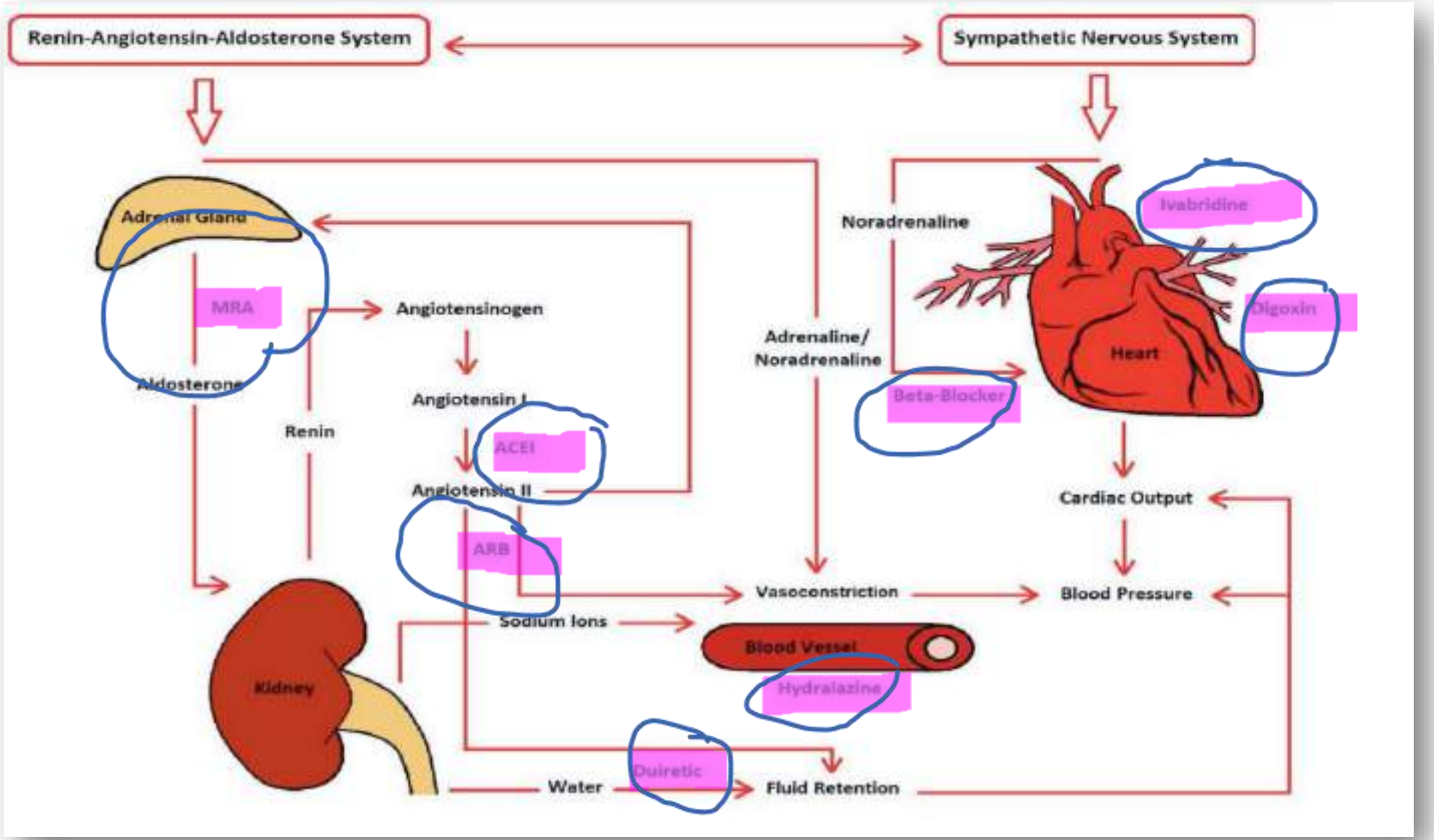
- **Cardiac contractility**
- **Preload: volume overload: cardiac dilatation**
- **Afterload: tension overload: cardiac hypertrophy**
- **Heart rate: tachycardia**

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**

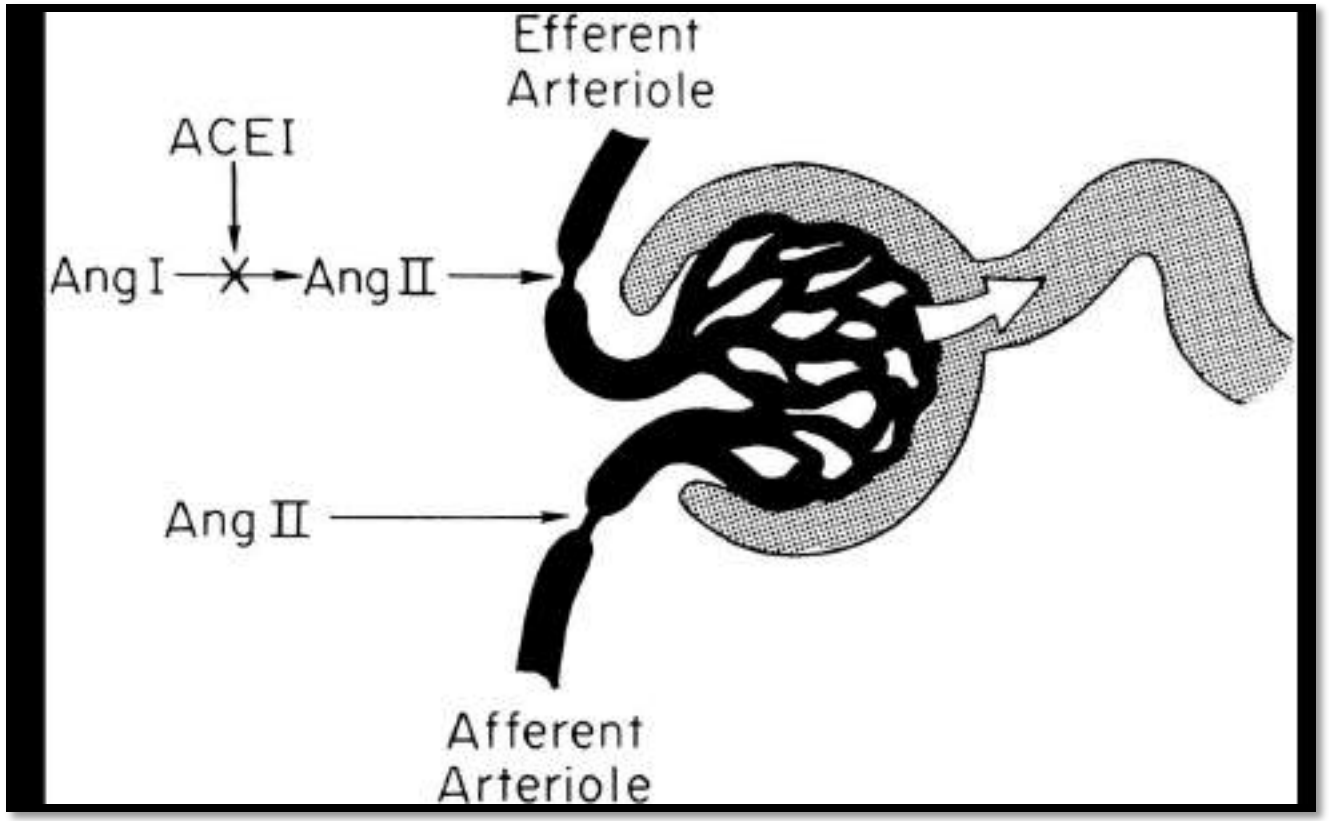
ACE Inhibitors & Angiotensin Receptor Blockers

- **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.**

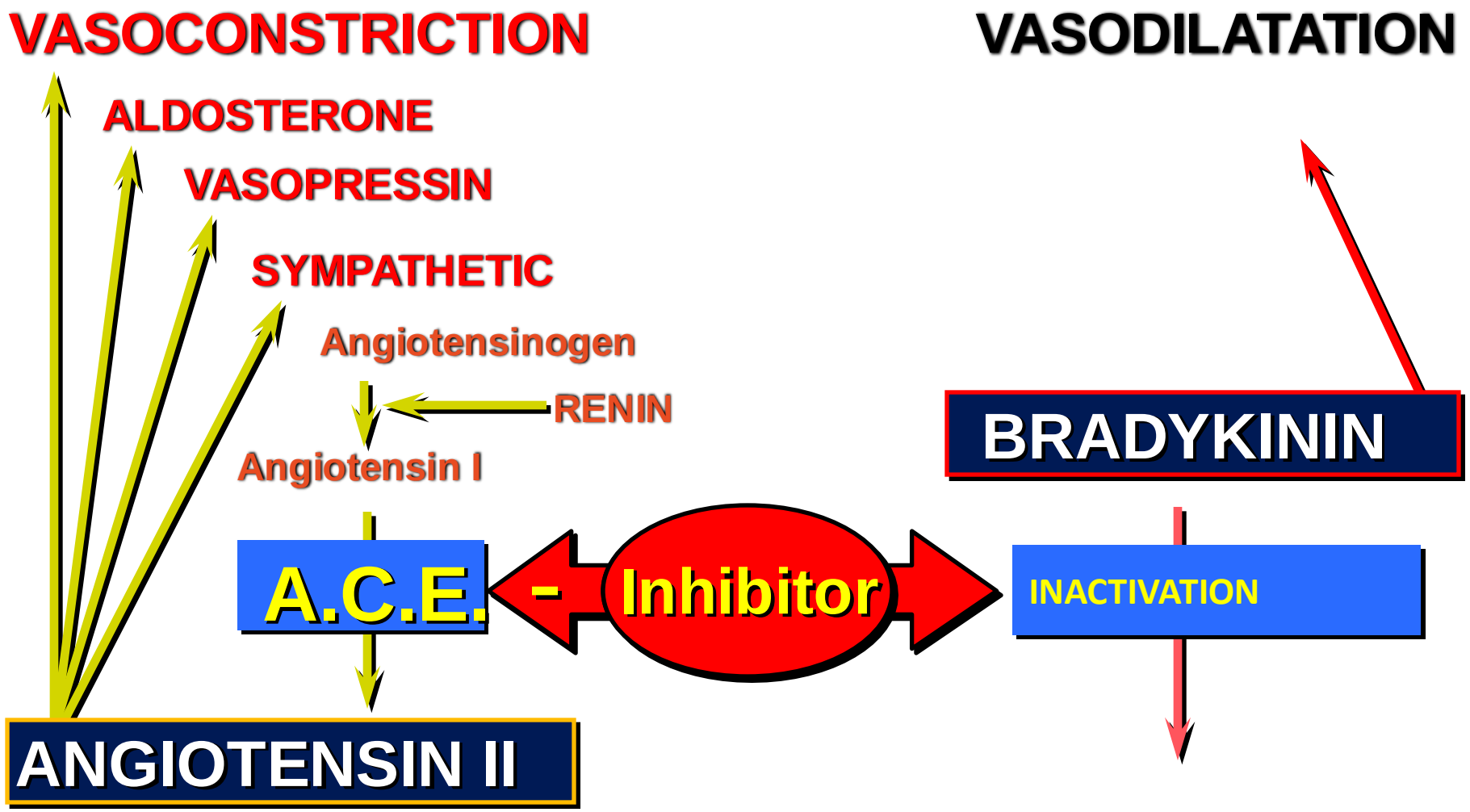
Effect of ACEIs on glomerular filtration

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.

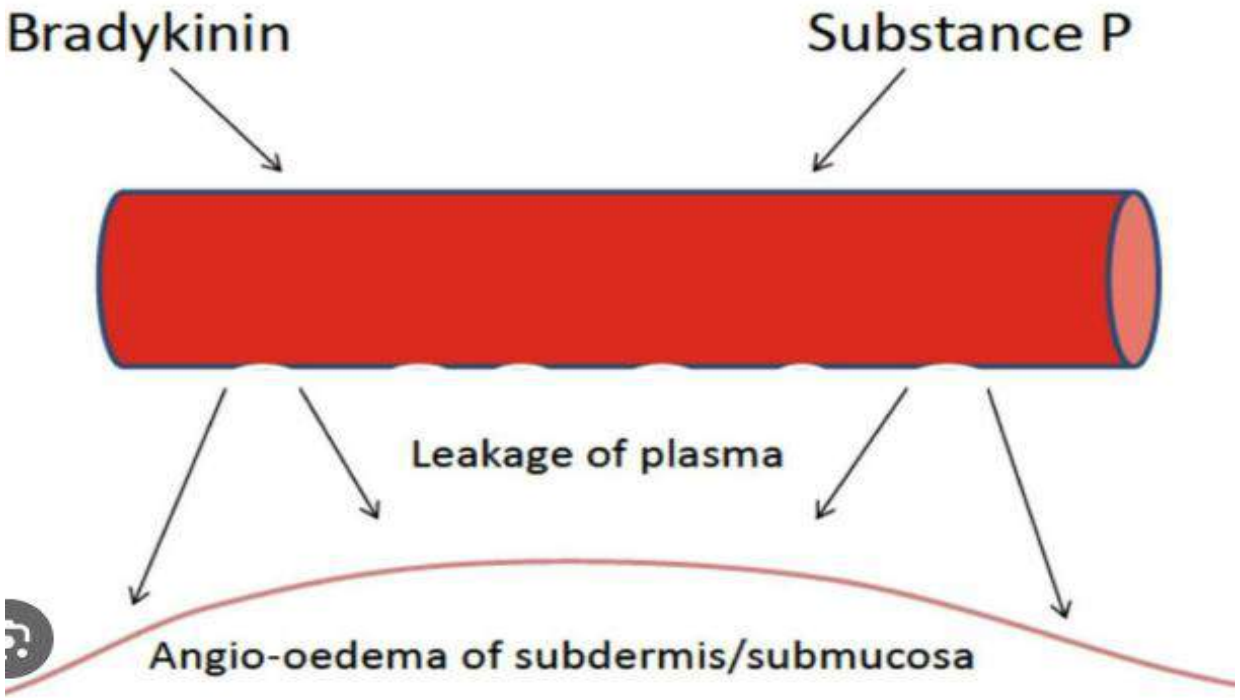


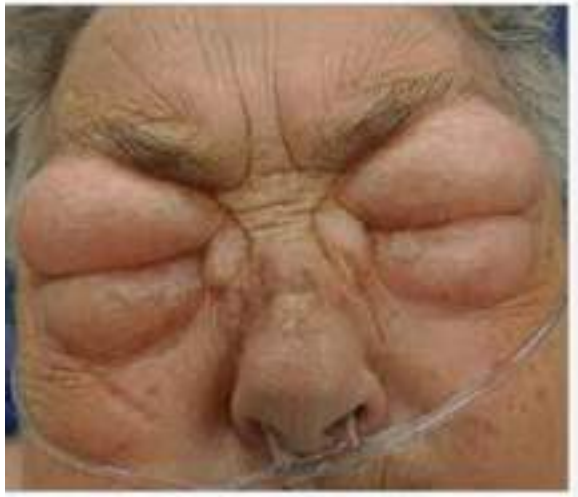
Angiotensin converting enzyme inhibitors

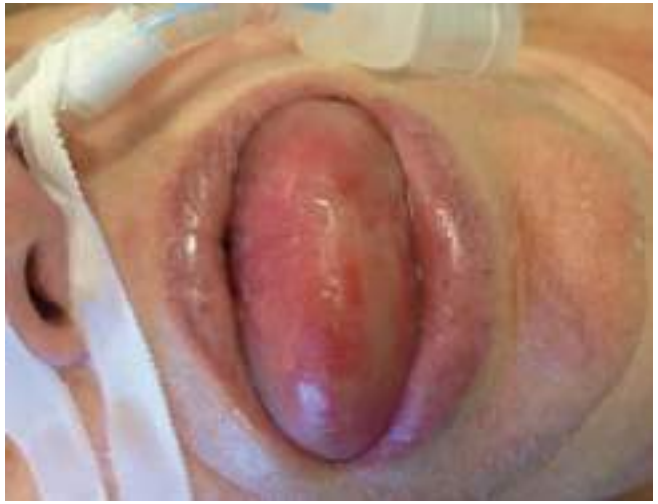
MECHANISM OF ACTION



Angioedema-induced ACEIs







Adverse effects of ACEIs

- 1- Teratogenic
- 2- Orthostatic hypotension
- 3- Potassium increase (hyperhalemia)
- 4- Cough (dry): 10%

Top card

- 5- Angioedema: 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- Renal impairment: increase creatinine level (**less than 30% accepted**)
- 7- Dizziness
- **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**

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 sever: 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):**

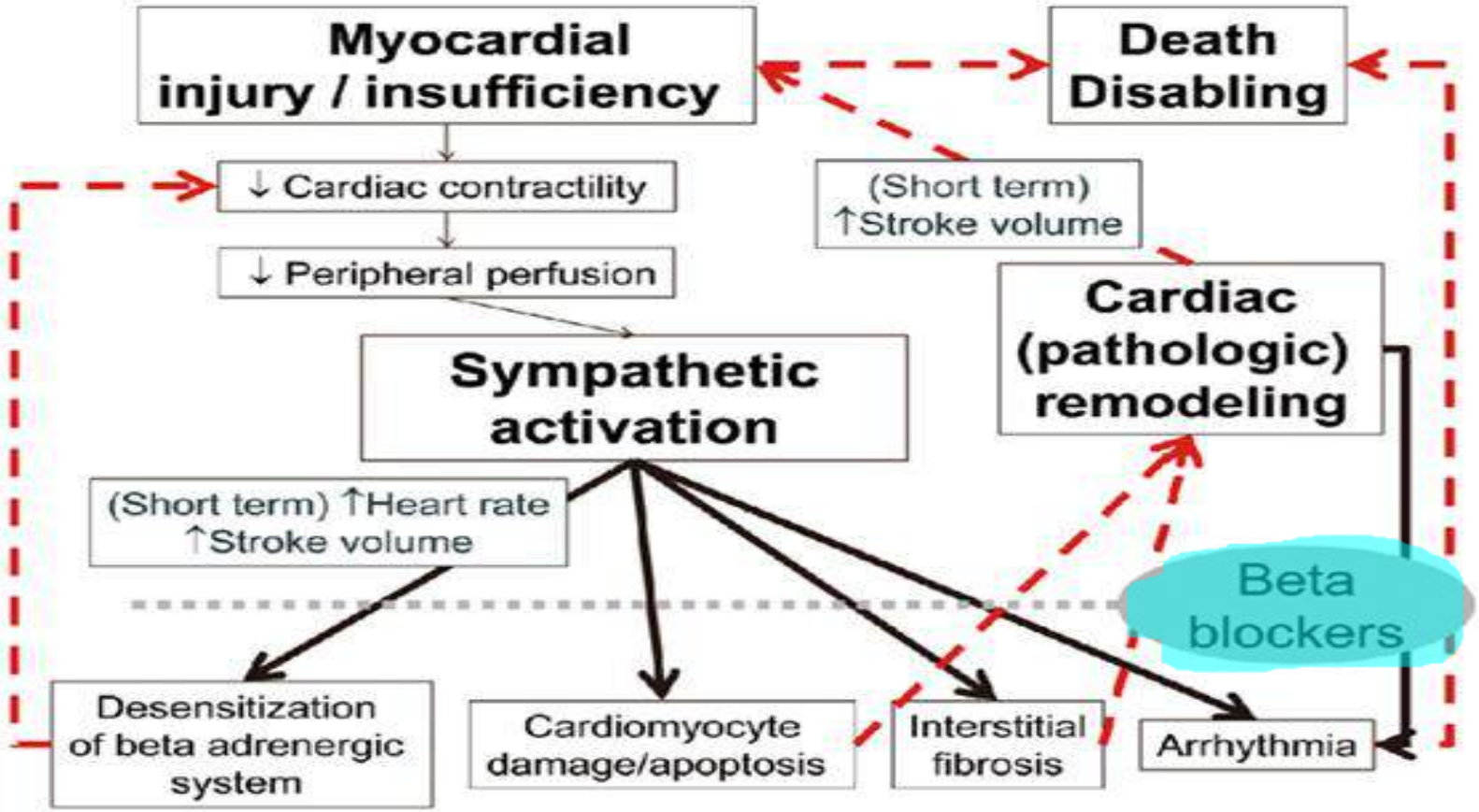
1- Bisoprolol

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



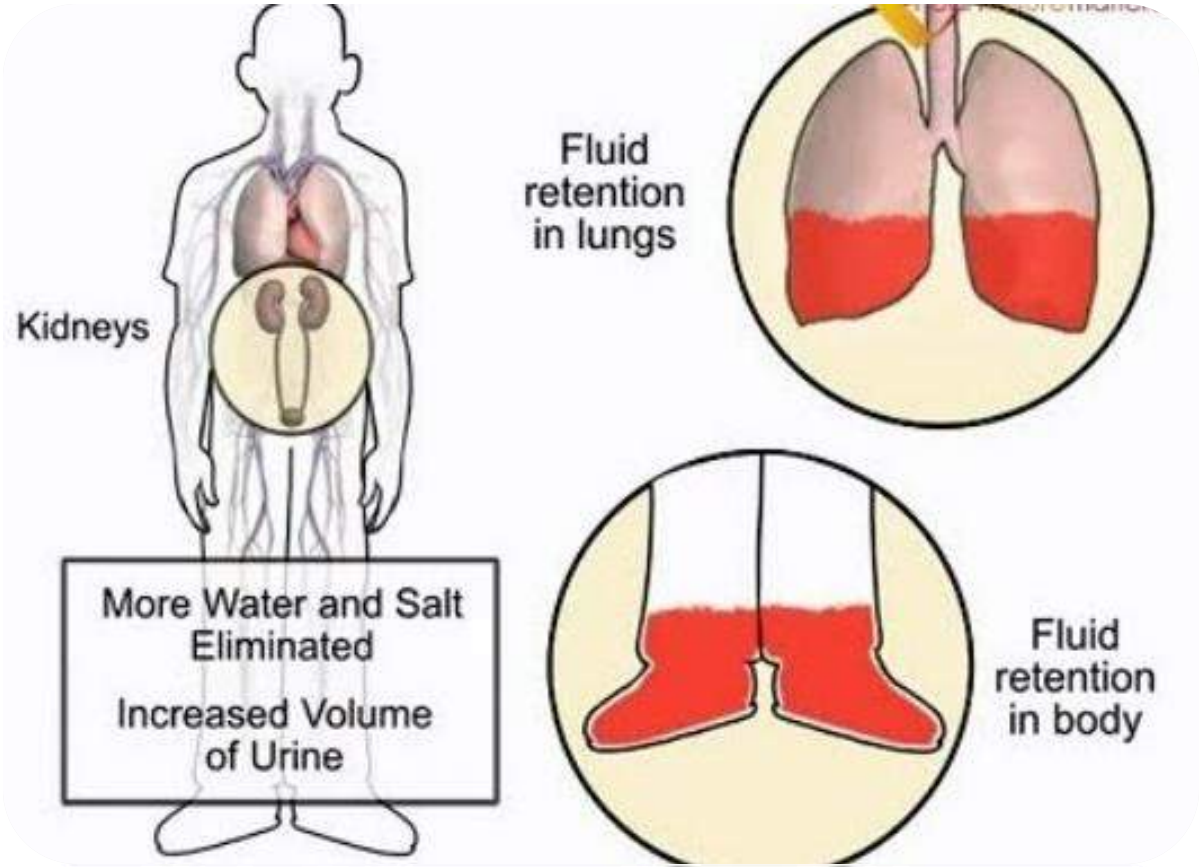
Diuretics

- **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, eplerenone:**
- are weak diuretics-for achieving volume reduction with minimal K^+ loss
- **Advantages of spironolactone:**
- 1- **Preserve potassium ion**: **prevents hypokalemia**
- **3- Reverse aldosterone-induced remodeling**
- 2- **Decreases mortality** in cases of sever HF
- **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 intolrant to ACEIs, ARBs**
- **Arteriolodilators: hydralazine**
- **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 over come 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:**

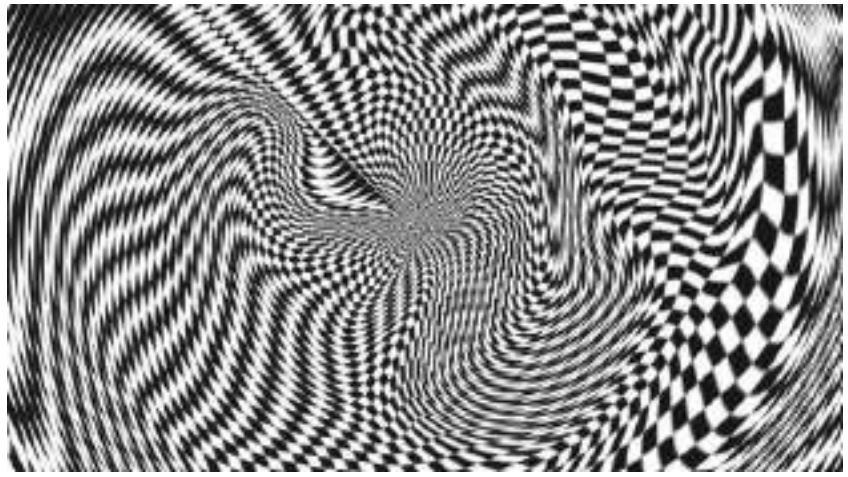
✓limited effect on systemic resistance

✓Nitrate tolerance

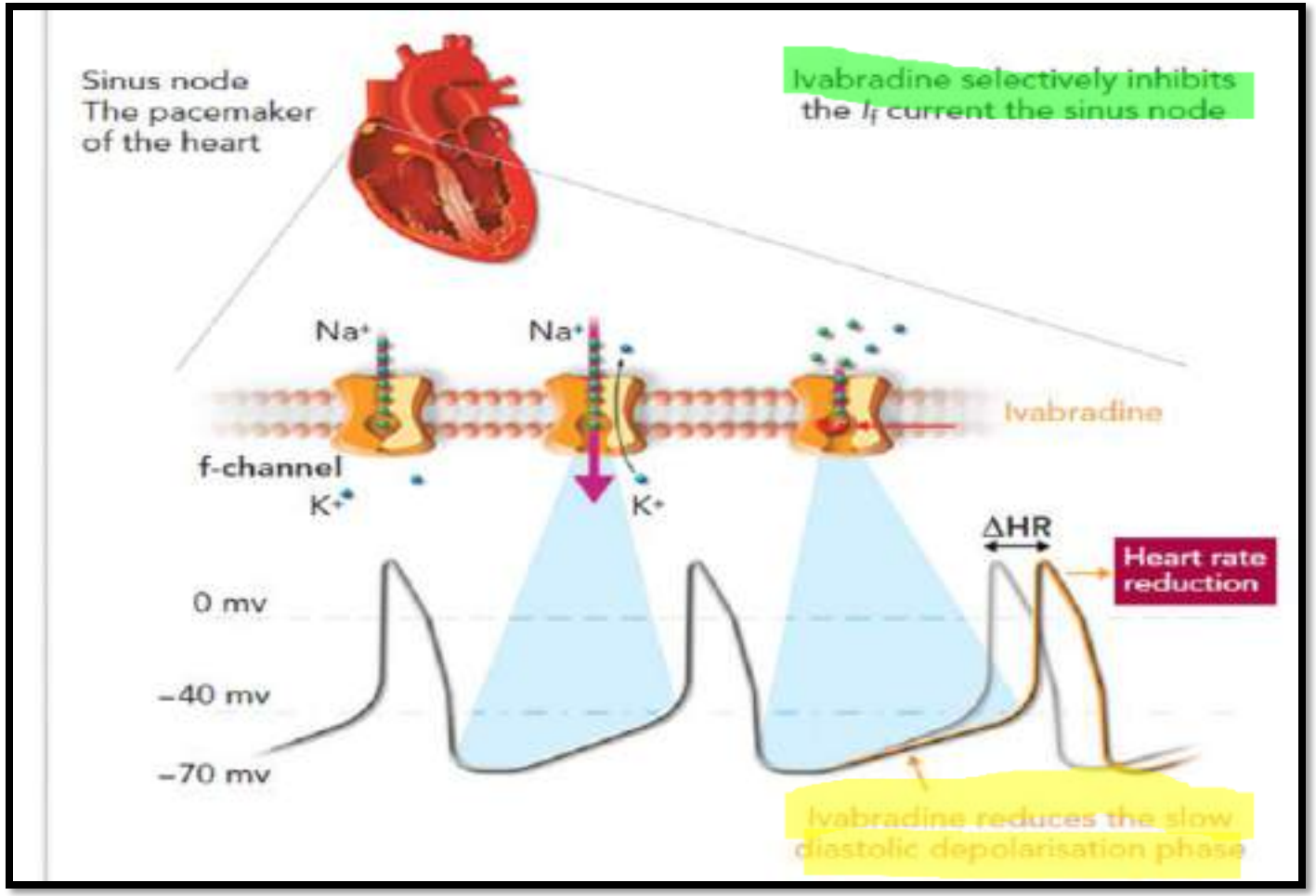
- **Often combined with other vasodilators for better results:**
- **Hydralazine/isosorbide dinitrate(Bidil)** is a fixed-dose combination: **improve mortality in some cases of HF.**

Ivabredine

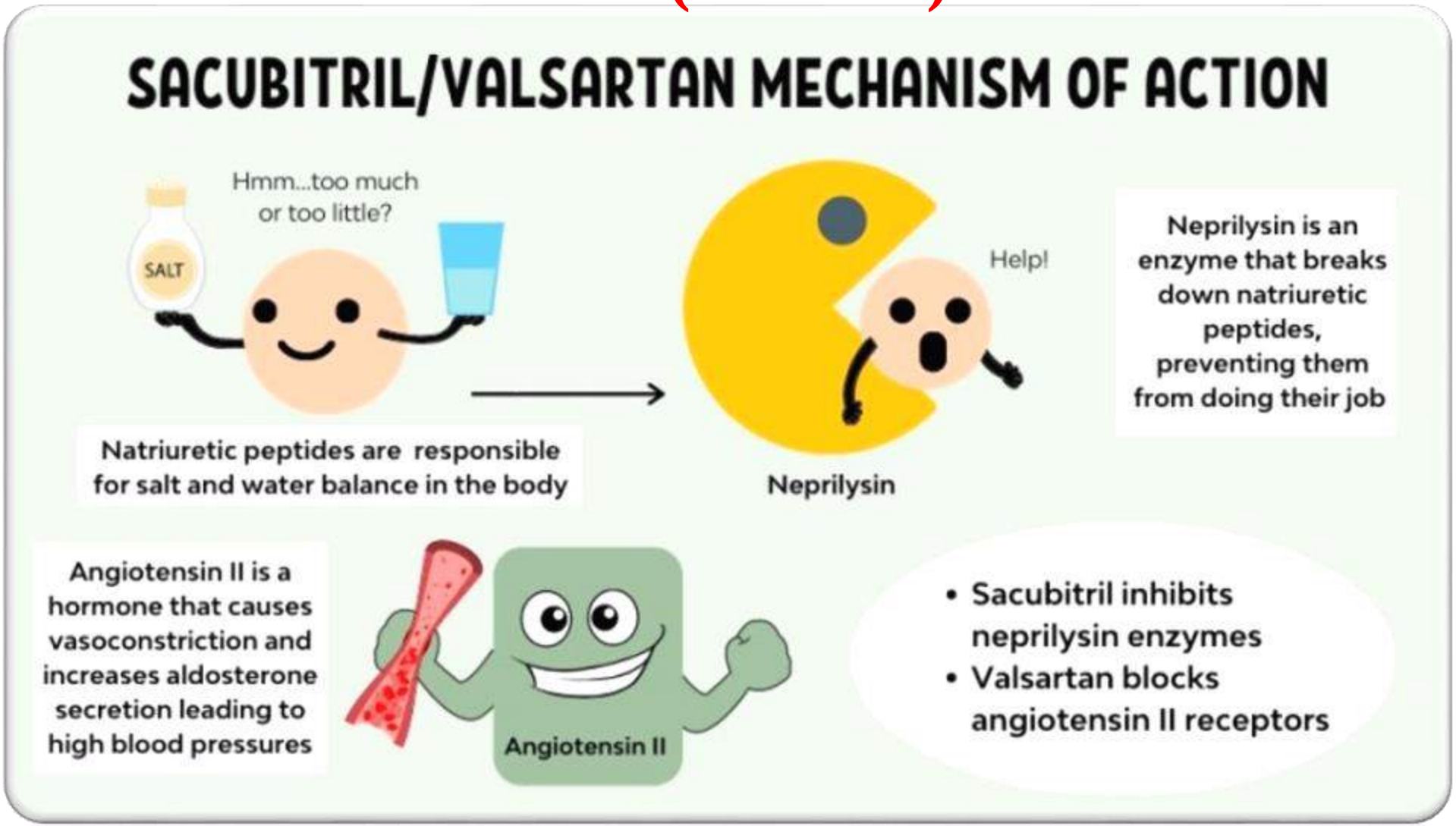
- **The First Selective and Specific I_f Inhibitor**
- **Blocks** the channel responsible for the **cardiac pacemaker spontaneous firing (funny channel), I(f)**, which regulates heart rate.
- **Without affecting any other cardiac ionic channels** (including calcium or potassium).
- **This results in 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 ivabredine



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



ARNI

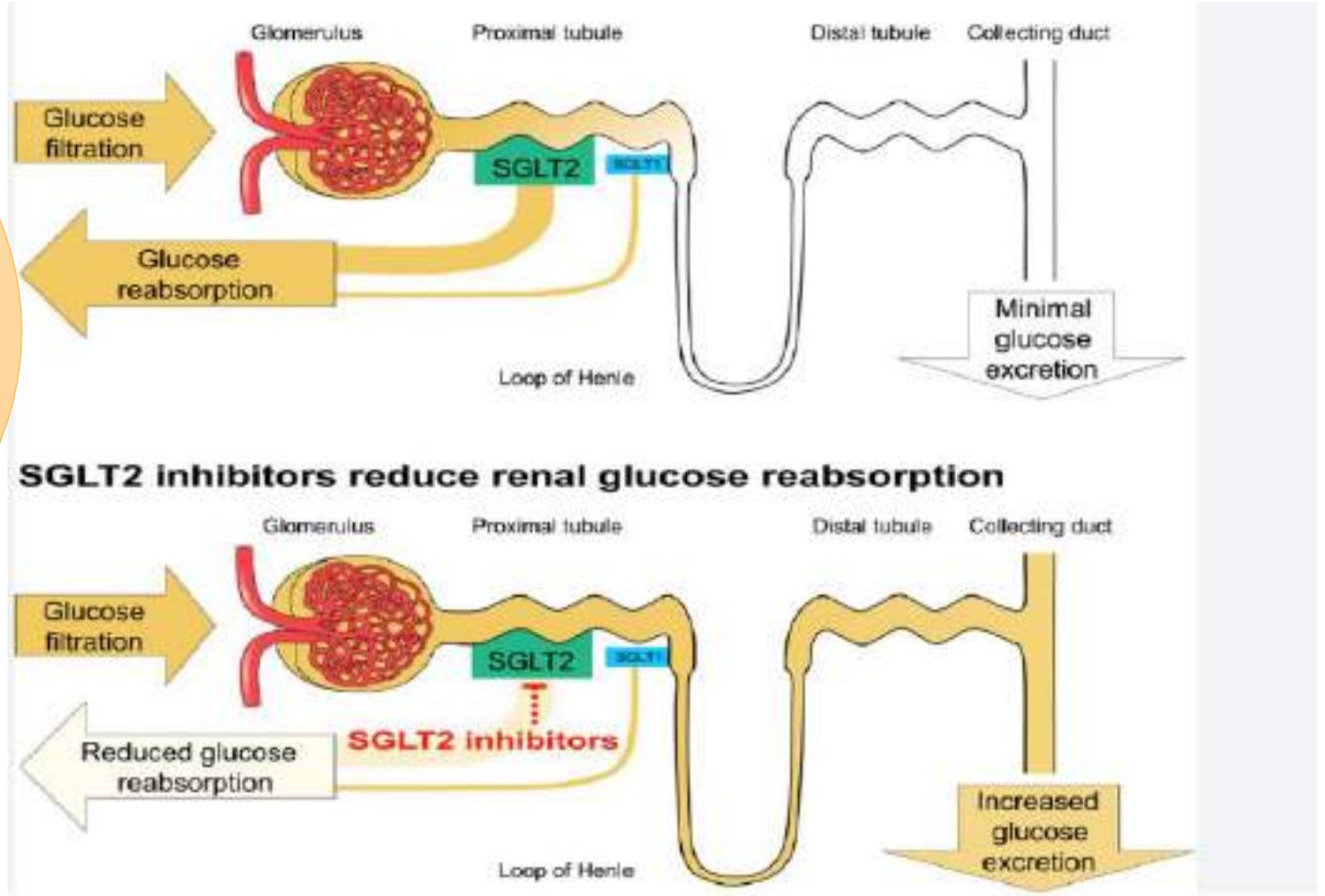
- **Adverse effects of Sacubitril-valsartan:**
- **Hypo**tension
- **Hyper**kalemia
- Renal failure
- **Indications:**
- ARNI new class of drugs indicated in **patients not responding to ACEIs or B blockers**

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- Reduced oxygen consumption by the kidneys.**
- **5- Reduction in sympathetic nervous system activity**

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

	Digoxin	Digitoxin
Protein Binding	Low (~20-30%)	High (~97%)
Elimination Half-life	Relatively short (approx. 1.5 - 2 days	Long (approx. 5 - 7 days)
Primary Elimination Route	Predominantly renal (excreted largely unchanged in urine)	Primarily hepatic metabolism and biliary excretion
Oral Absorption	Less complete: 80%	Complete: >90%

Inotropic Drugs

Cardiac glycosides: Digoxin

William Withering
1785

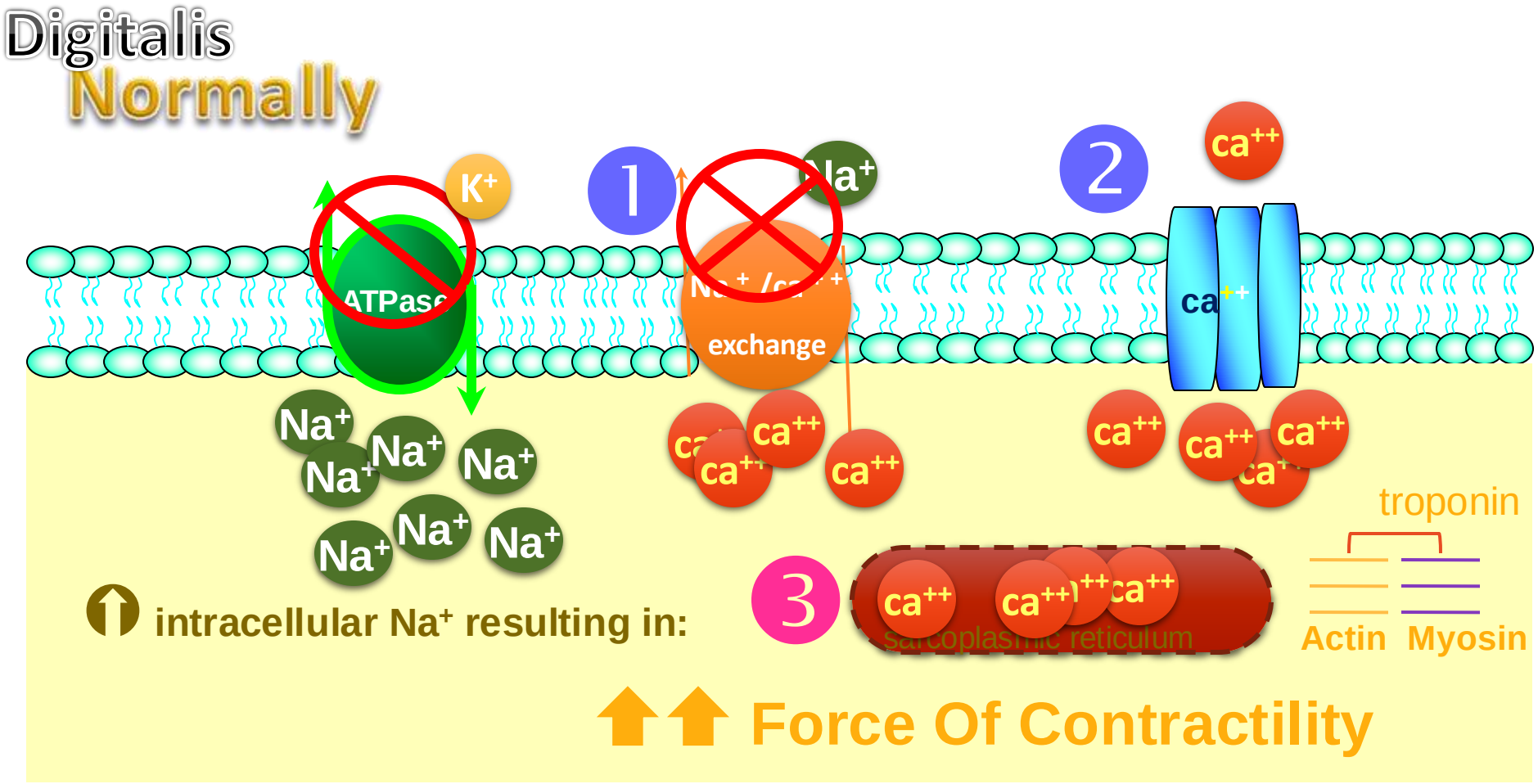
Foxglove plant

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 (**vagal effect**): ↑ 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 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 Na+/K+ ATPase (reversible partial inhibition)** by competition **with K+** , So **hypokalemia increase Digitalis toxicity** , while K+ administration improve toxicity of digitalis.

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: (decreasing AV node CV)**

- 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: 2X2X2 or 2X3X1**

•**Then maintenance dose**

Contraindications

Absolute

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

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, cholystramine**: decrease digitalis absorption
- **2- Quinidine**: decreases digitalis clearance
- **3- K- losing diuretics**: increase digitalis toxicity

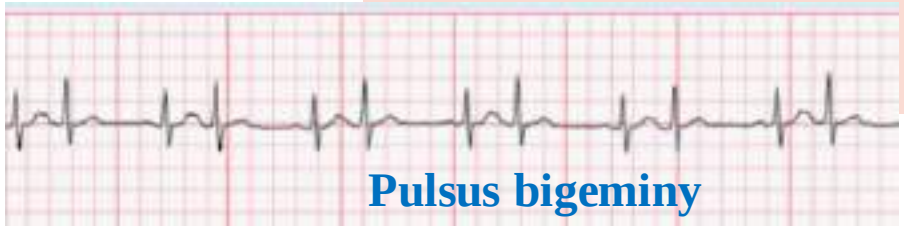
Toxicity of digoxin

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



Pulsus bigeminy

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

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Thank you ❤