Drug therapy of congestive heart failure

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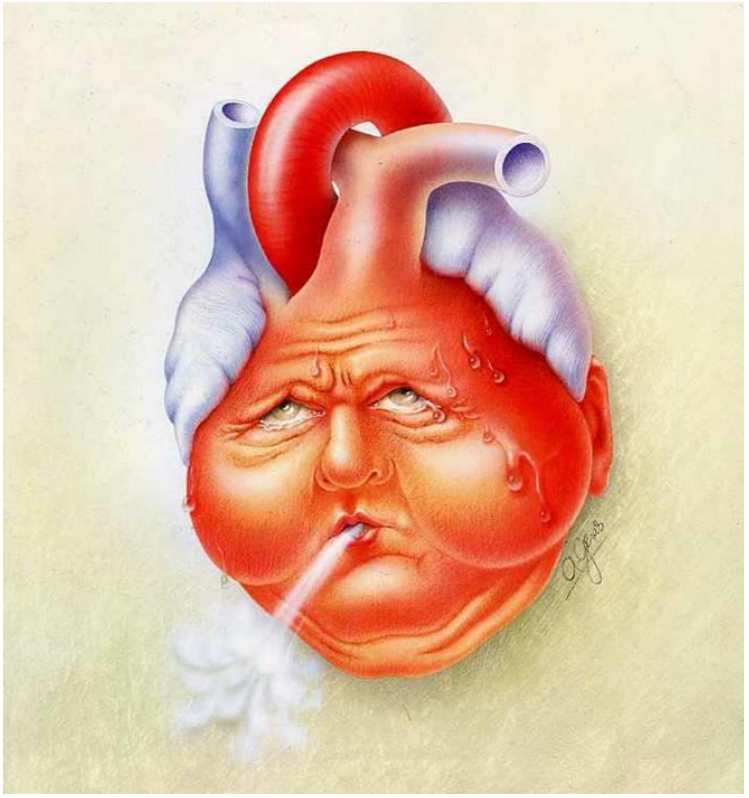


Objectives

- 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- Explain mechanism of action of digitalis and its major effects
- 4- Explain the nature and mechanism of digitalis toxic effects
- 5- Ivabredine and ARNIs
- 6- SGLT-2 Inhibitors: Canagliflozin
- 7- Describe the strategies used in the treatment of heart failure
- 8- Approach to management of HF

What is heart failure?

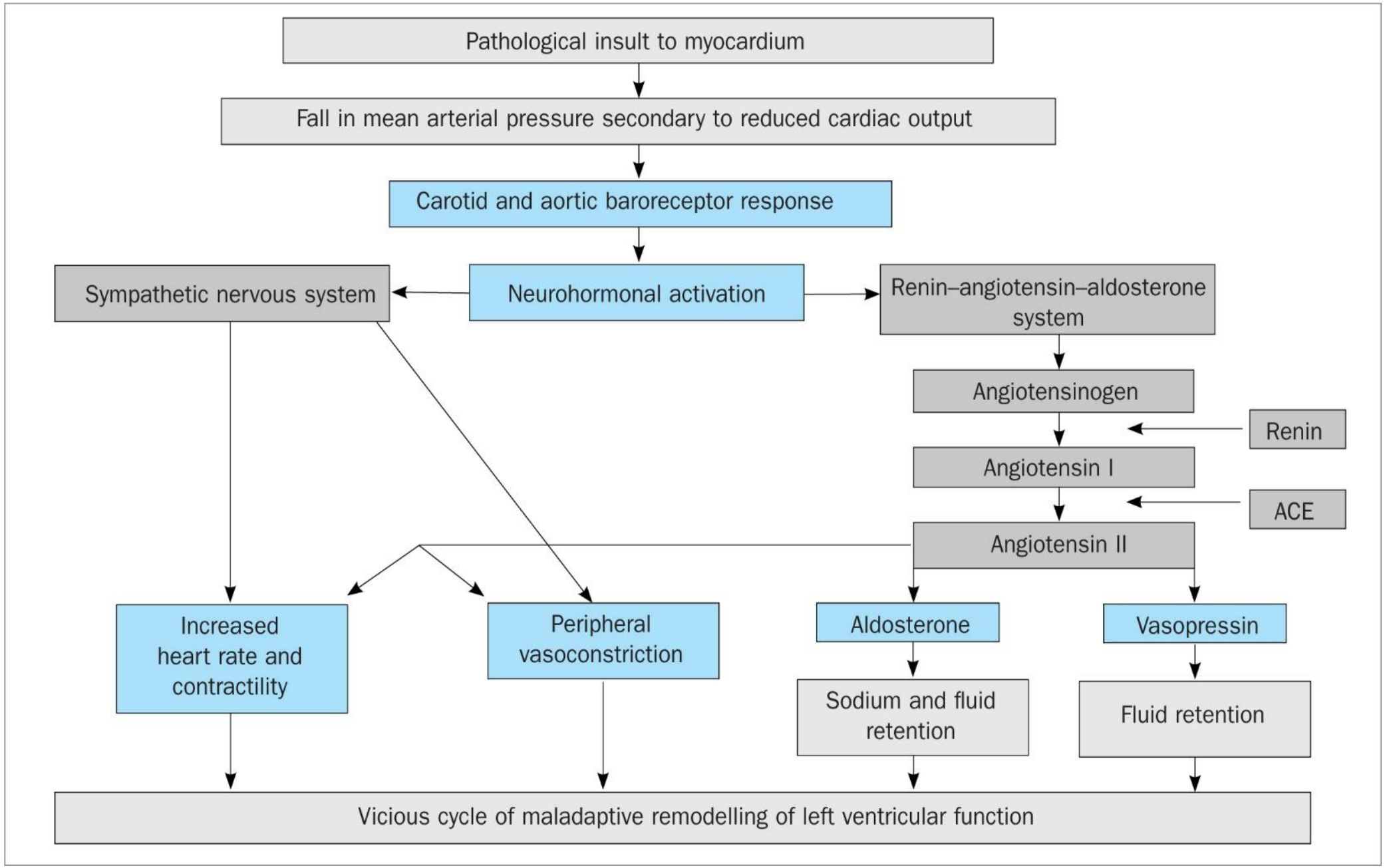
- **Inability of the heart to maintain sufficient cardiac output inspite of good venous return.**
- Heart failure (HF) is a **complex clinical syndrome (not a disease)** that can result from any **structural** or **functional** cardiac disorder that impairs the ability of the ventricle to **fill** with or **eject** blood.
- **Types of HF according to ejection fraction (EF = SV/EDV):**
- **Systolic HF: HFrEF**
- **Diastolic HF: HFpEF**

Causes of HF (classification)

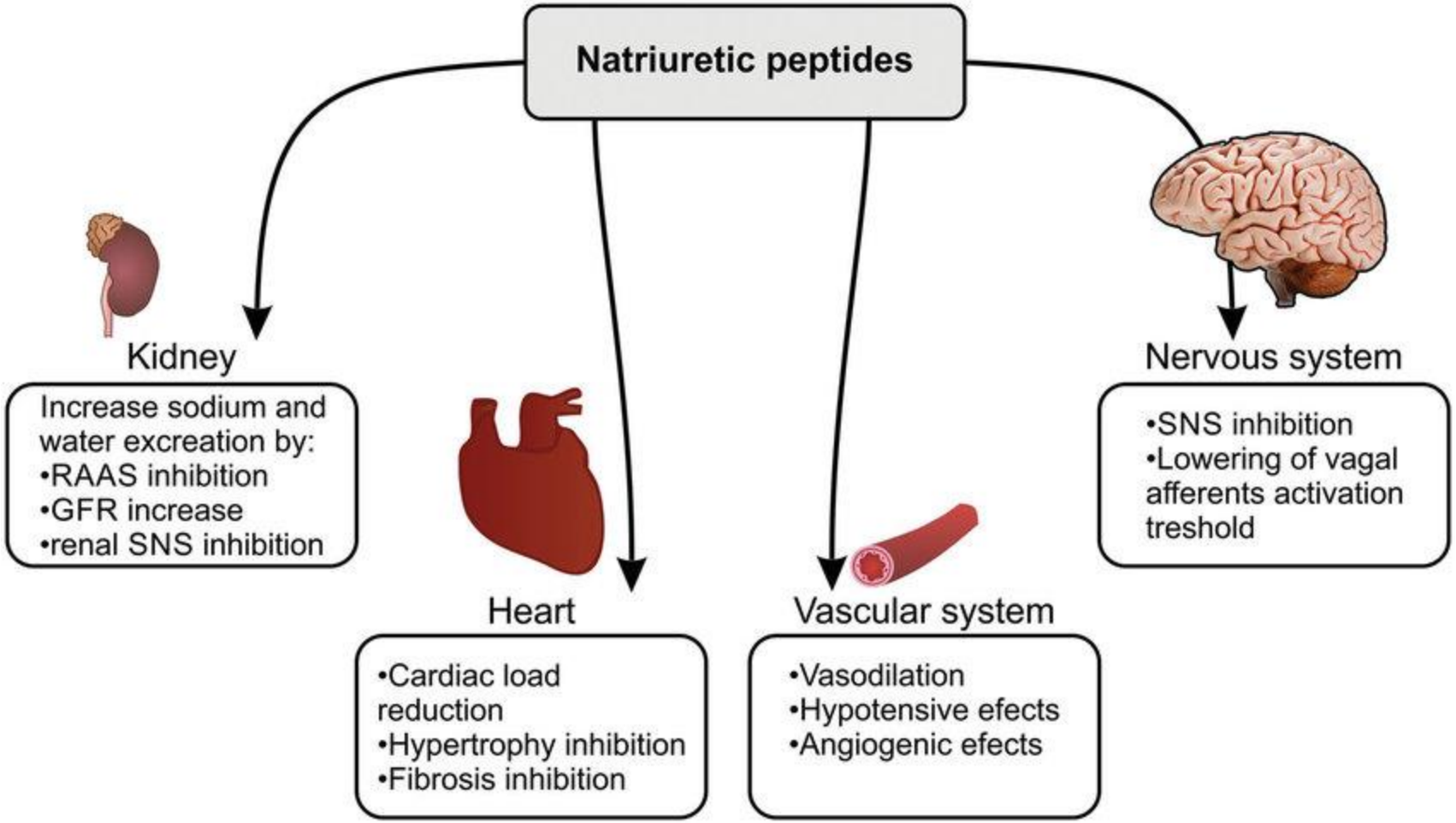
Etiology	Left-sided HF	Right-sised HF
Increased preload	AR, MR, VSD, hyperdynamic circulation	TR, PR, VSD, hyperdynamic circulation
Increased afterload	AS, Aortic cortication, systemic hypertension	PS, Pulmonary hypertension, COPD
Decreased contractility	Coronary ischemia, cardiomyopathy, myocarditis	

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


Pathological insult to myocardium
Fall in mean arterial pressure secondary to reduced cardiac output
Carotid and aortic baroreceptor response
Sympathetic nervous system
Neurohormonal activation
Renin–angiotensin–aldosterone system
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Increased heart rate and contractility
Peripheral vasoconstriction
Aldosterone
Vasopressin
Sodium and fluid retention
Fluid retention
Vicious cycle of maladaptive remodelling of left ventricular function

Activation of natriuretic peptide system in HF

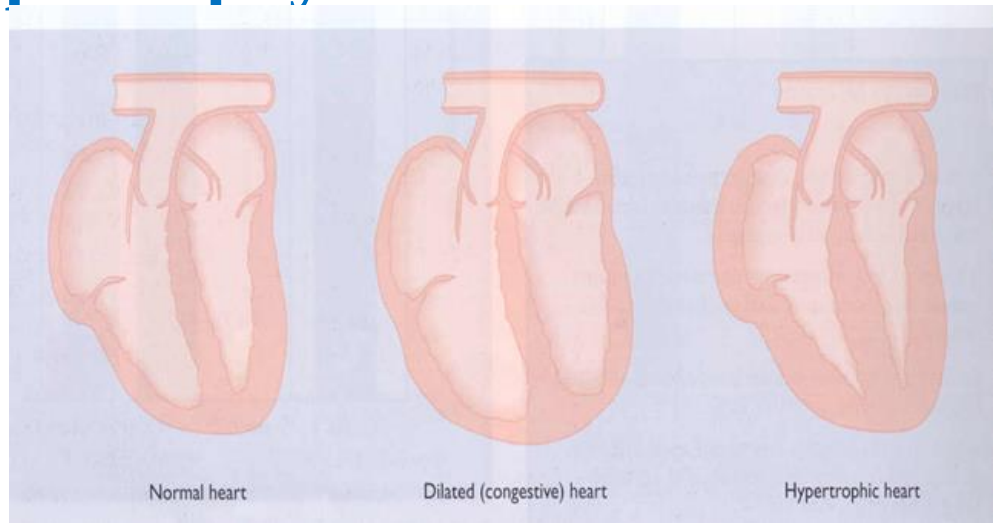


Diagnostic Criteria Of HF

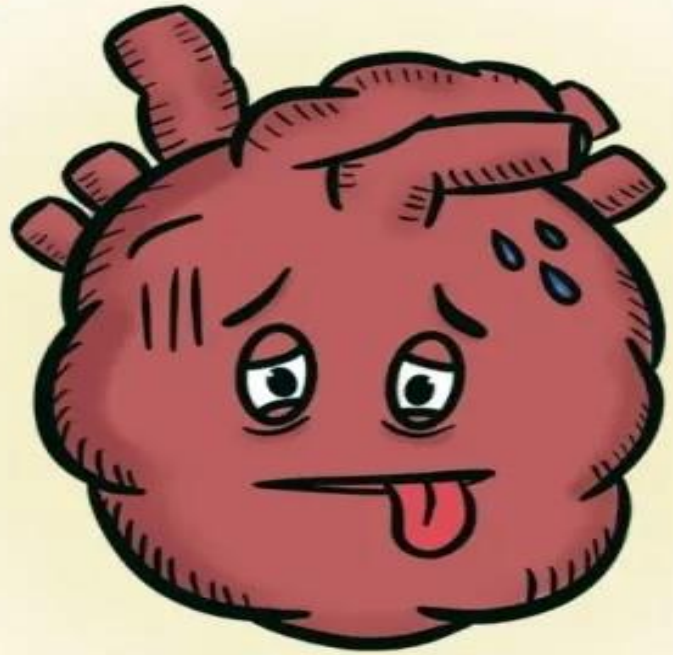
- **Triade of:**
- **Symptoms: shortness of breath, physical fatigue**
- **Signs: tachycardia, tachypnea, edema**
- **Evidence of structural or functional abnormality of heart, example: cardiomegaly**

Factors Affecting Cardiac Output And Heart Failure

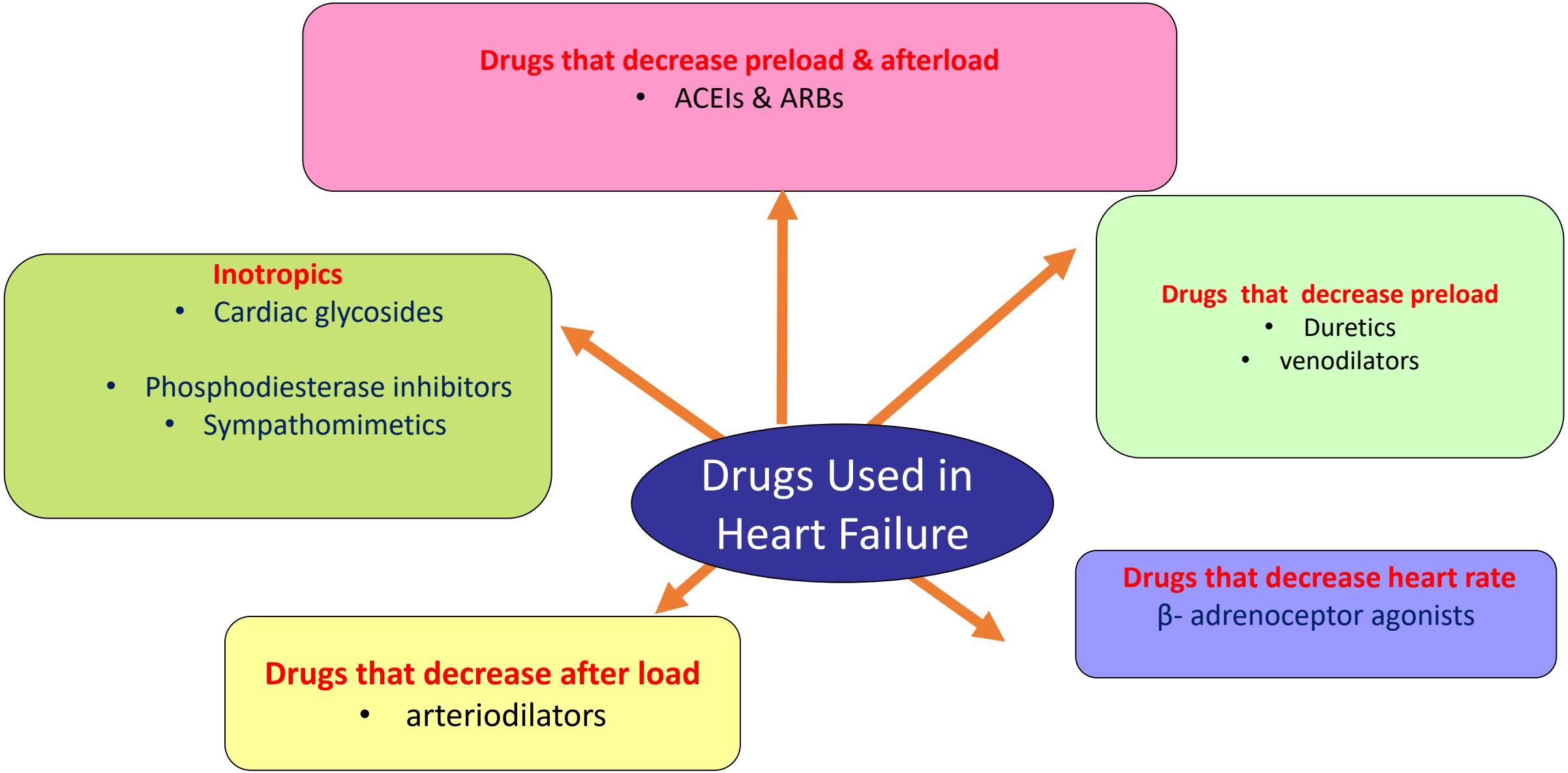
- **Cardiac contractility**
- **Preload: volume overload: cardiac dilatation**
- **Afterload: tension overload: cardiac hypertrophy**
- **Heart rate: tachycardia**



HEART FAILURE



DRUGS


Drugs that decrease preload & afterload
• ACEIs & ARBs
Inotropics
• Cardiac glycosides
• Phosphodiesterase inhibitors
• Sympathomimetics
Drugs that decrease preload
• Duretics
• venodilators
Drugs Used in Heart Failure
Drugs that decrease after load
• arteriodilators
Drugs that decrease heart rate
β- adrenoceptor agonists

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**

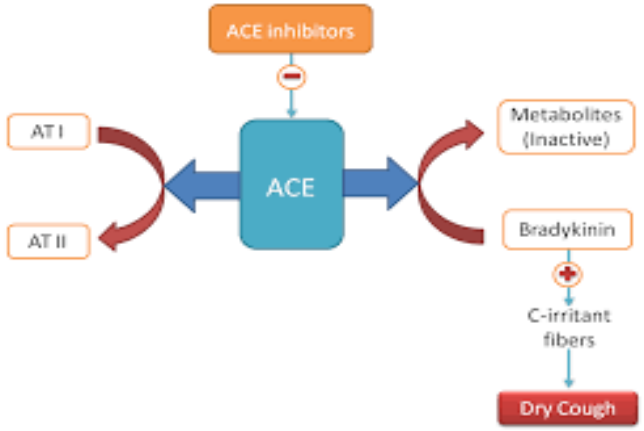
- **First line drugs for HF with volume overload (edema and congestion):**
- **Diuretics and positive inotropic drugs**

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**

Adverse effects of ACEIs

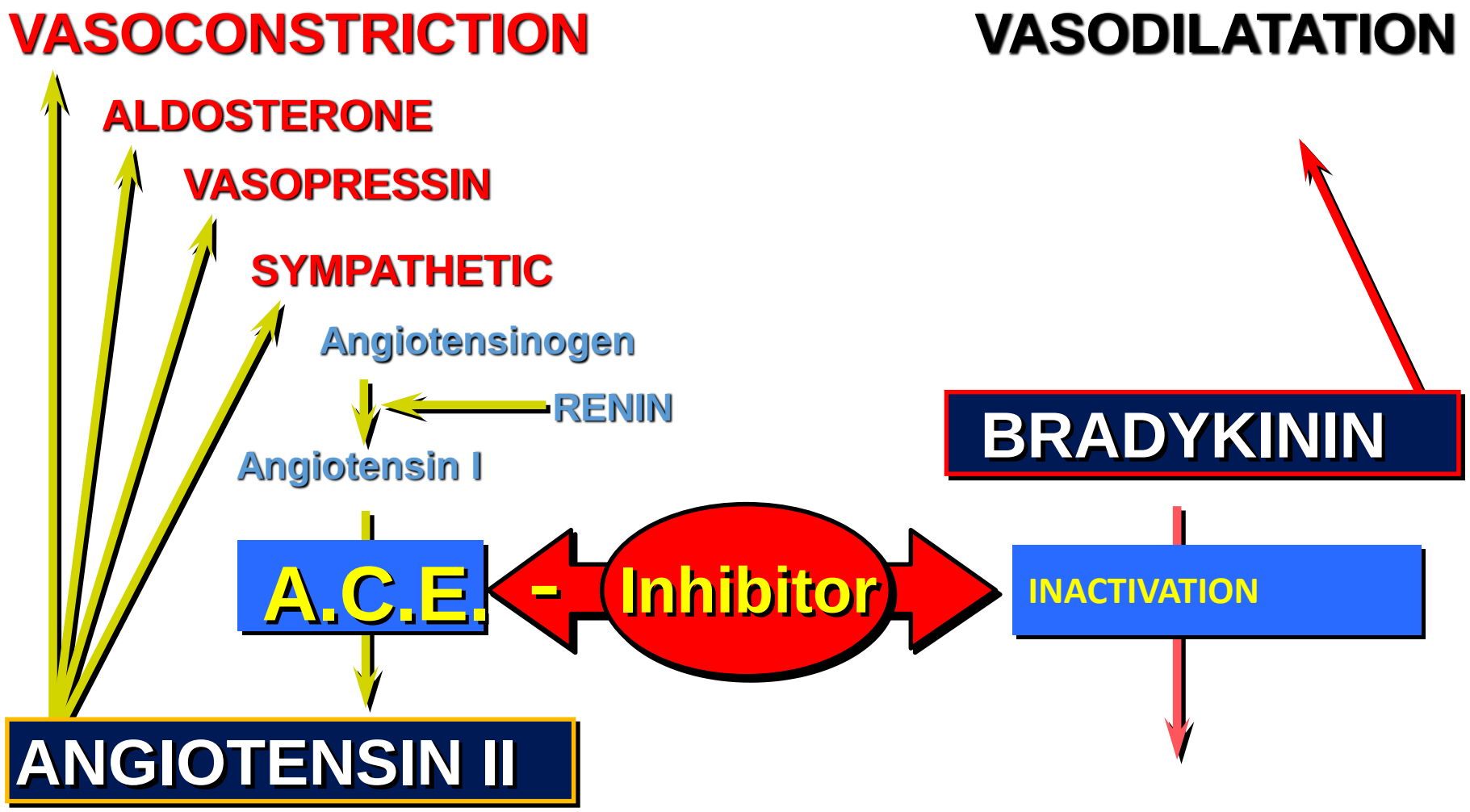
- 1- Dry cough: 10%
- 2- Headach
- 3- Hypotension
- 4- Angioedema: rare



- Dry cough and angioedema are due to elevated plasma bradykinins.
- **ARBs**: less effective and typically used in patients who can not tolerate ACEIs.

Angiotensin converting enzyme inhibitors

MECHANISM OF ACTION



B-adrenoceptor Blockers In Heart Failure

- **Benefits in HF:**
- **Reduce catecholamine myocyte toxicity (remodeling)**
- **Inhibit renin release**
- **Decrease heart rate**
- **Decrease mortality rate**
- **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)

Vasodilators

- **Indications of vasodilators in HF:**
- **pateints intorant to ACEIs, ARBs**
- **Arteriolodilators**: 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
- **Preferred drug in CHF (ACE intolerant) with renal impairment**

Venodilators: nitrates

- **How nitrates are helpful in CHF?**
- Reduce preload
- Coronary artery dilatation- reperfusion
- **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 motrality in some cases of HF.

Diuretics

- **Among First-line therapy of heart failure**
- **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)

•Spironolactone, triamterene, amiloride are weak diuretics-for achieving volume reduction with minimal K^+ loss

•**Advantages of spironolactone**:

•1- Preserve K: prevents hypokalemia

•2- Decreases mortality in cases of sever 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**

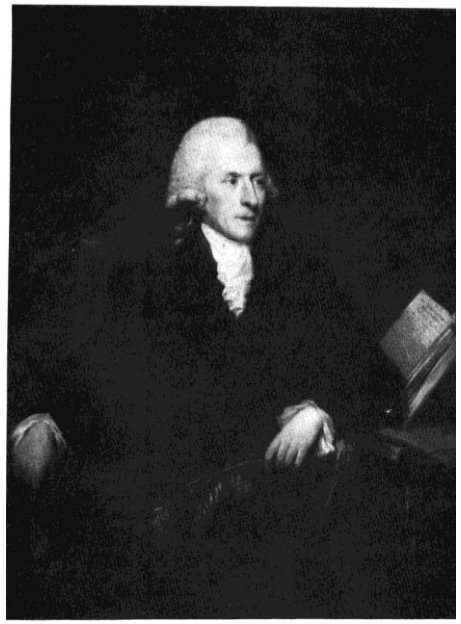
Drugs That Increase Contractility

Inotropic Drugs

- **Cardiac glycosides:**
- Digoxin, digitoxin
- **Phosphodiesterase inhibitors:**
- Amrinone , milrinone

Inotropic Drugs

- **Cardiac glycosides: Digoxin**



William Withering 1785

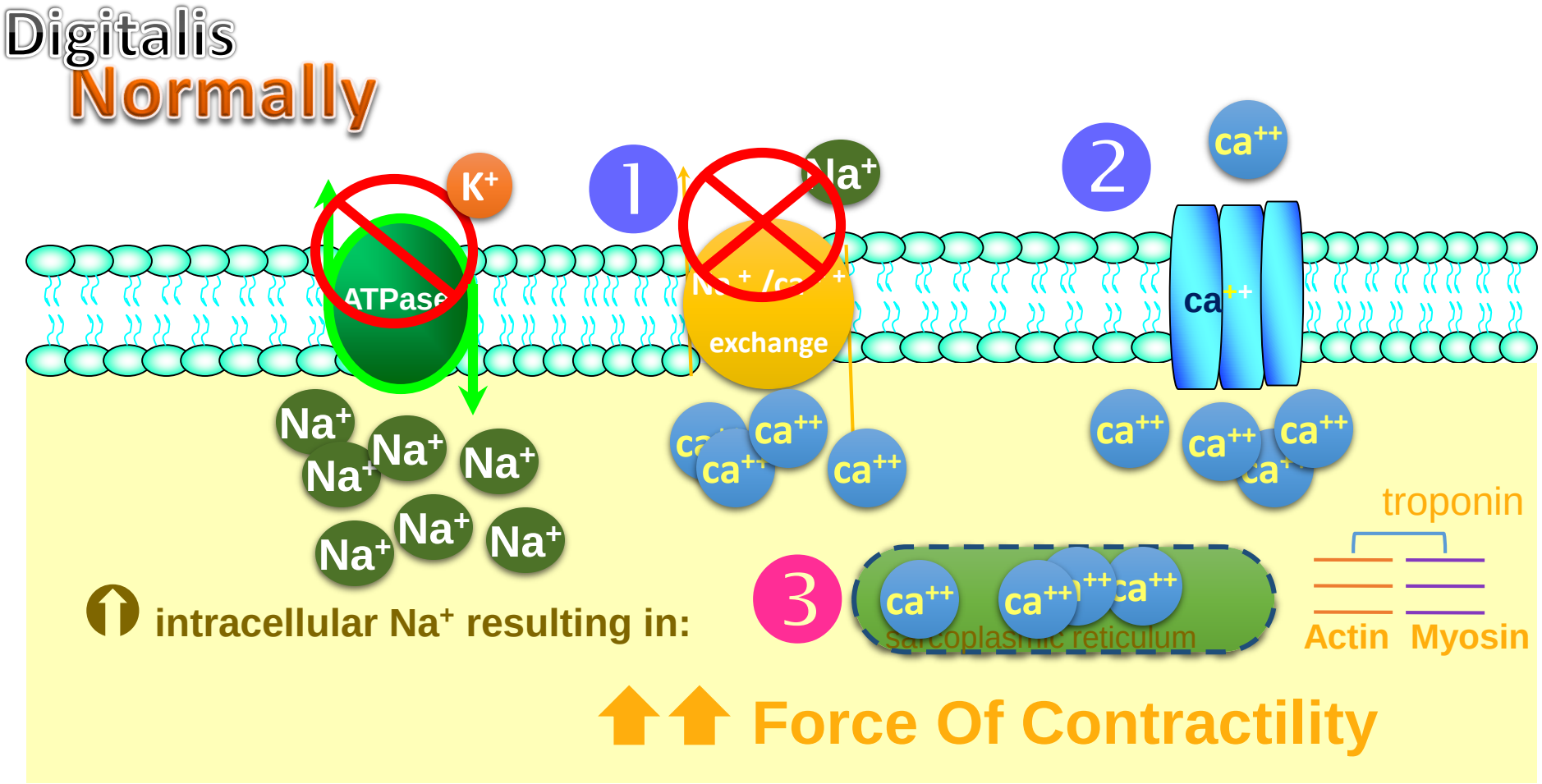
Foxglove plant

Beneficial Effects Of Digoxin In HF

- **(Increasing the contractile force of the cardiac muscles)**
- **<u>This effect is manifested in patients with heart failure, this results in:</u>**
- 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

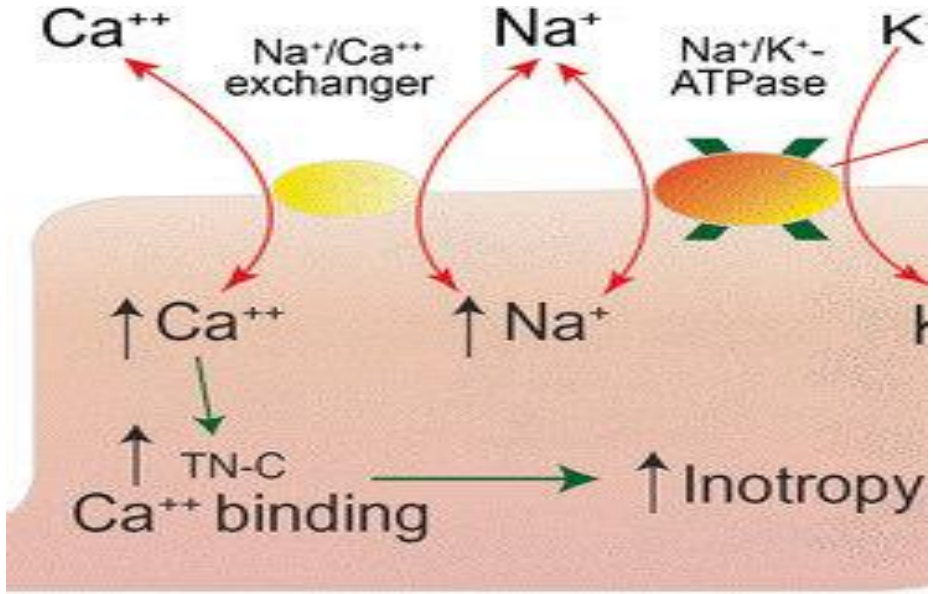


Digitalis Mechanism Of Action

- **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 by competition **with K+** , So **hypokalemia increase Digitalis toxicity** , while K+ administration improve toxicity of digitalis.
- In therapeutic dose leads to **partial inhibition** of Na^+/K^+ ATPase enzyme

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

- **1- Inhibition of membrane bound Na+ K+ Atpase enzyme**: ↑ increasing intracellular Na+ → ↑ 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

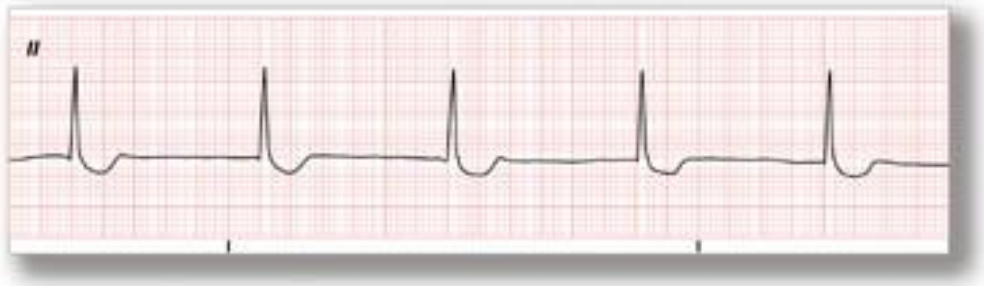
CARDIAC

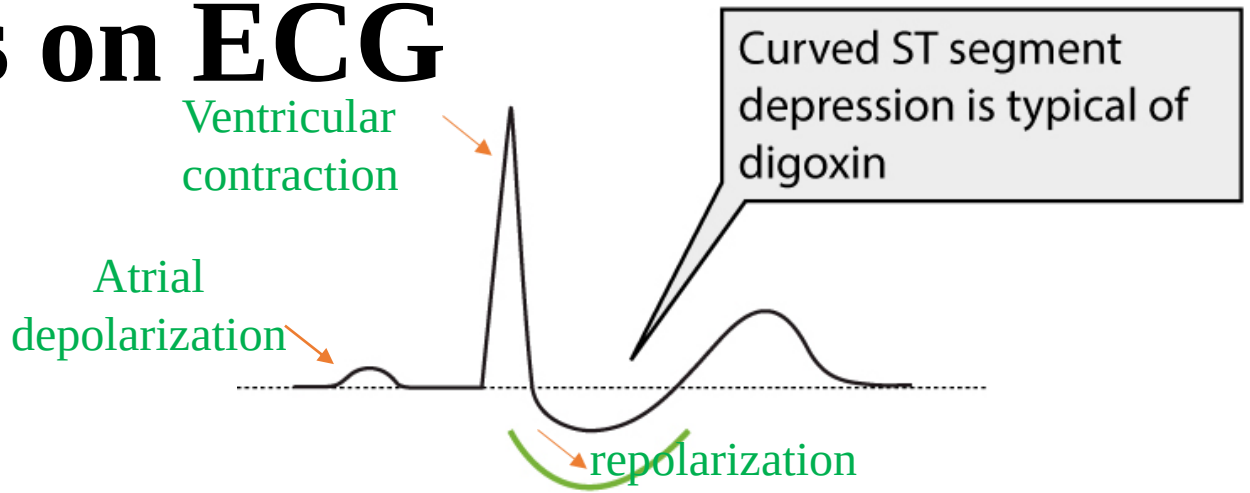
- Contractility: ↑force of contraction & Cardiac Output: +ve inotropic
- ↓ Heart rate : - ve chronotropic: vagal stimulation: by direct and indirect mechanisms
- Conductivity: - ve dromotropic↓ CV in AV node
- Increased automaticity: ectopic foci
- Increased excitability: arrhythmia
- Rhythmicity: disturbed

EXTRA CARDIAC

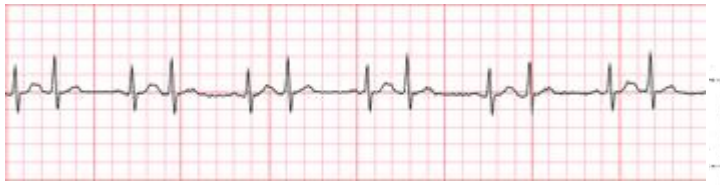
- Kidney:
- Due to improvement in circulation and renal perfusion
- Retained salt and water is gradually excreted
- CNS:
- Nausea, vomiting

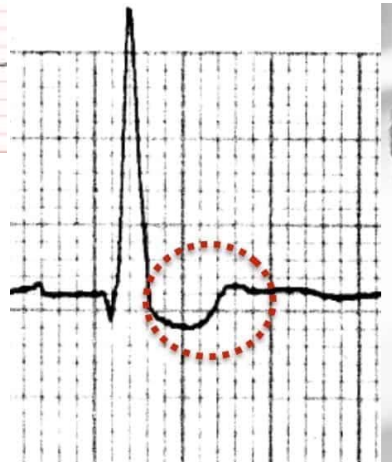
Digitalis effects on ECG

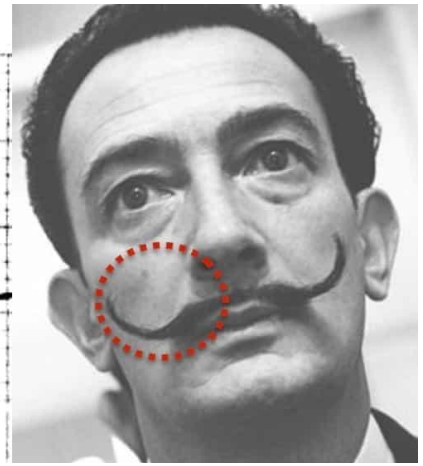




- ECG: not indicator of toxicity but indicates treatment with digitalis.
- 1- Prolongation of P-R interval
- 2- High R wave
- 3- Depressed S-T segment
- 4- Inverted T- wave
- 5- Bradycardia
- 6- Any type of ahrrythmia: pulsus bigemini or trigemini







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

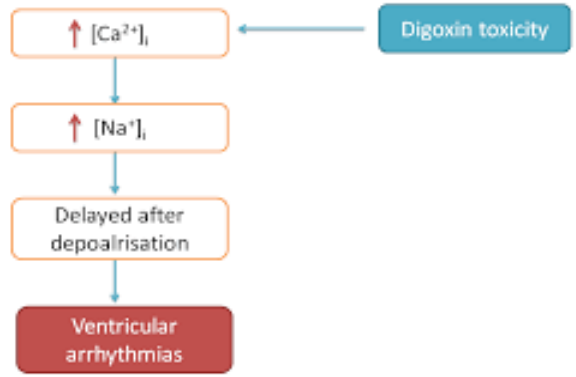
Toxicity of digoxin

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 Increase Digitalis Toxicity

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

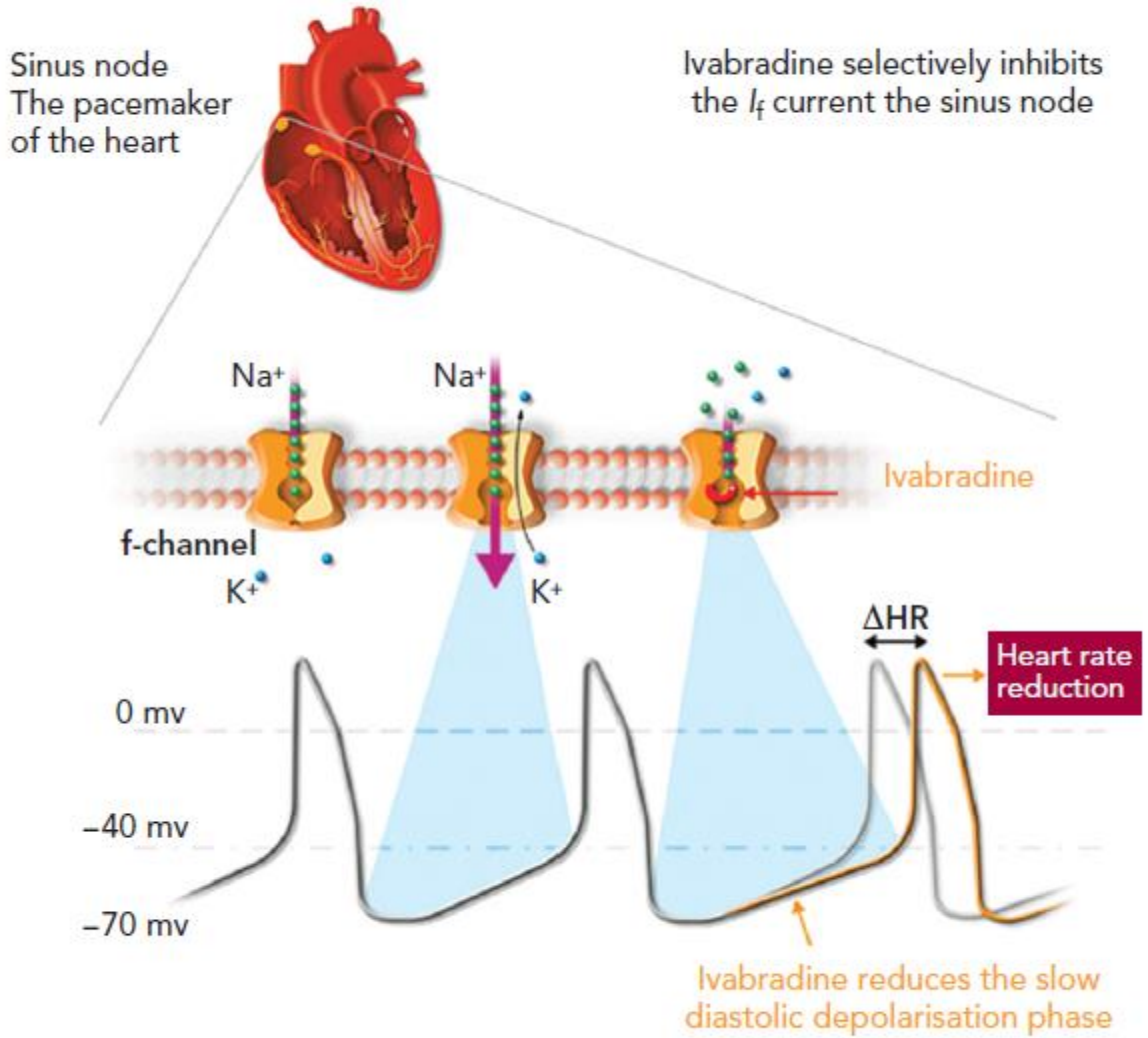
Treatment Of Digitalis Toxicity

- **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**: (digibind) **FAB fragment life saving: most spesific**

Ivabredine

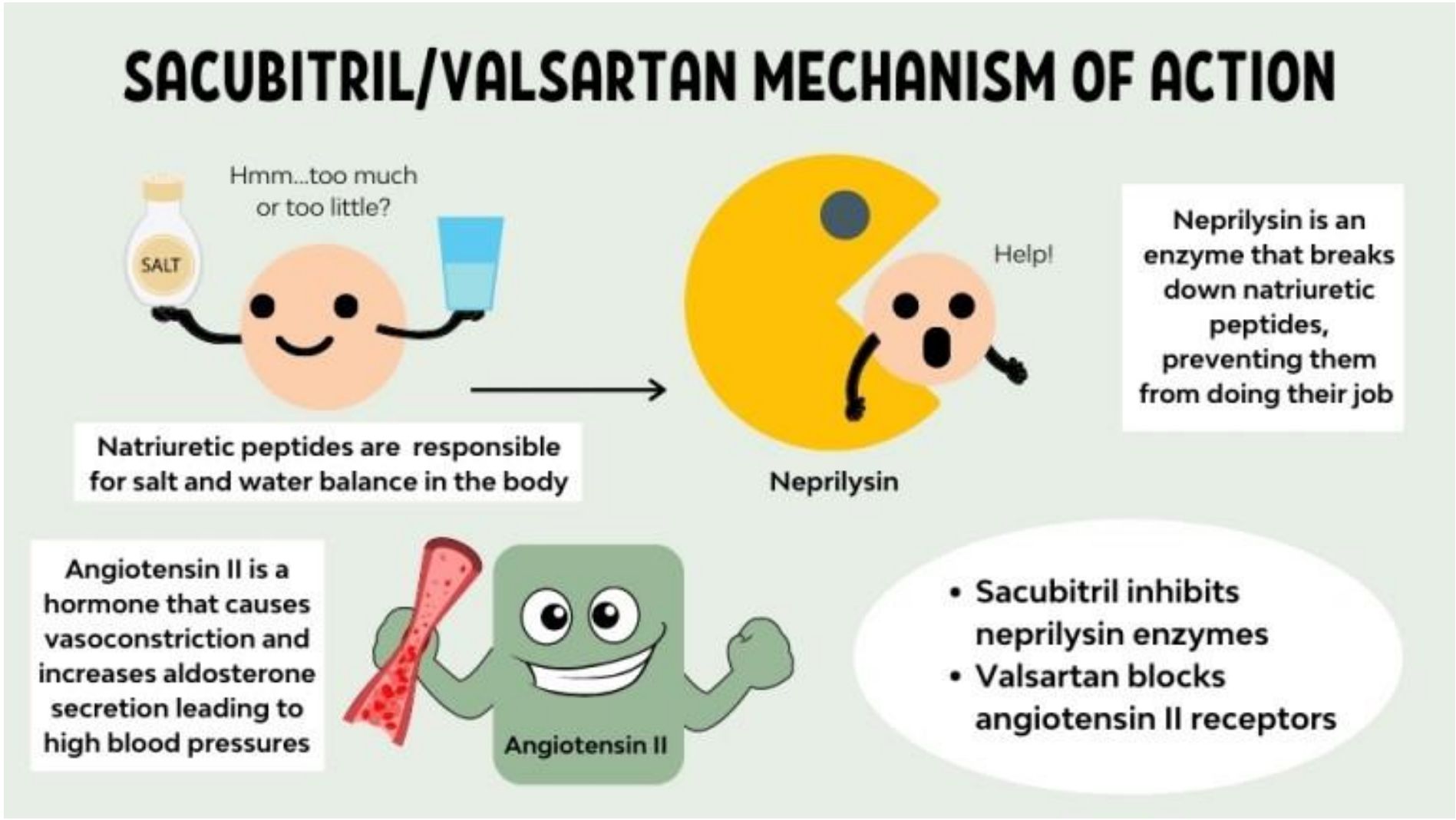
- **The First Selective and Specific I_f Inhibitor**
- Blocks the channel responsible for the cardiac pacemaker spontaneous firing (funny channel), I(f), which regulates heart rate.
- Without affecting any other cardiac ionic channels (including calcium or potassium).
- This results in reduced heart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

Figure 1: Mechanism of Action of Ivabradine



Source: http://www.shift-study.com/ivrabradine/mode-of-action/ Reproduced with the permission of Servier © 2016.

ARNI (angiotensin receptor/neprilysin inhibitor)

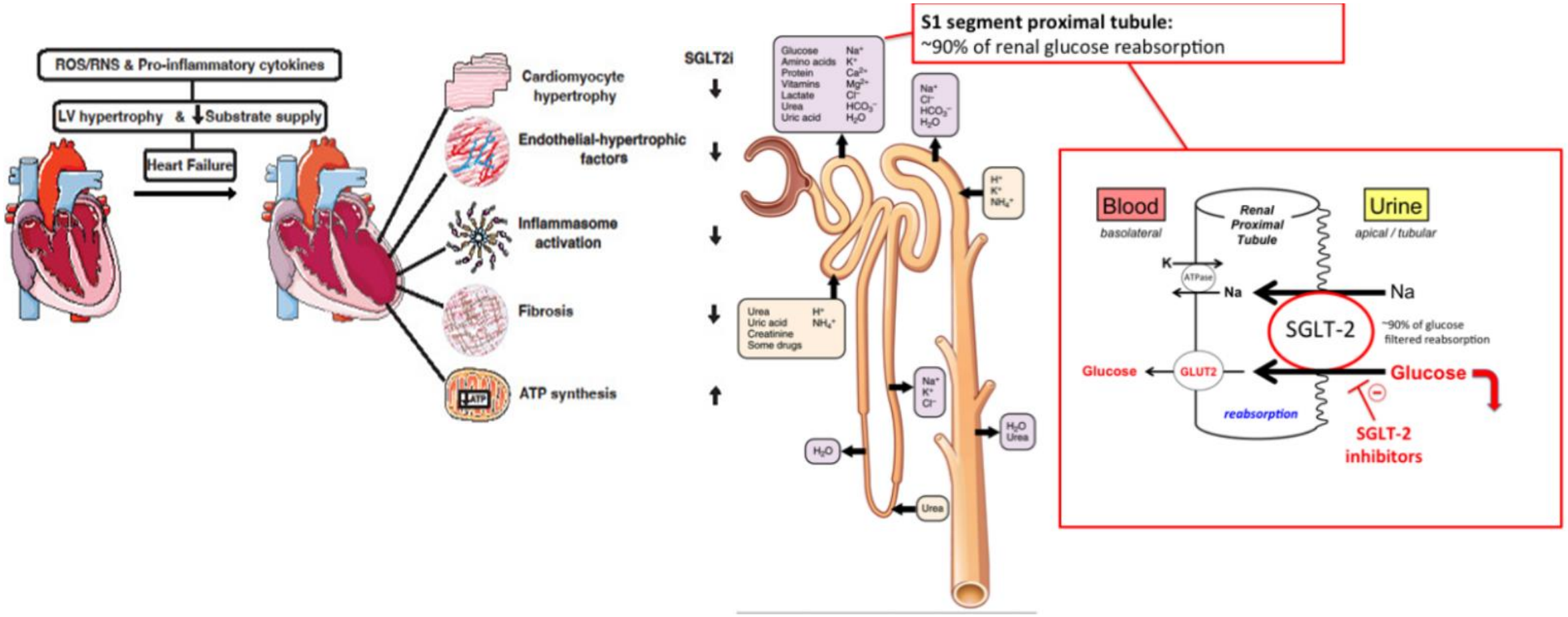


- **Adverse effects of Sacubitril-valsartan:**
- Hypotension, hyperkalemia and renal failure
- **Indications**:
- ARNI new class of drugs indicated in patients not responding to ACEIs or B blockers

SGLT-2 Inhibitors
Canagliflozin

- **Mechanism of Action:**
- **Inhibits the Na-glucose co-transporter 2 (SGLT-2)** in the kidney to reduce glucose reabsorption, resulting in increased urinary glucose excretion, and lower plasma glucose.
- **SGLT-2** is expressed in the proximal tubule and **mediates reabsorption of ~90% of filtered glucose** .
- **SGLT2 inhibition appears to underlie the ability of "gliflozins" to produce additional effects in the reduction of mortality and CV events in patients with heart failure.**

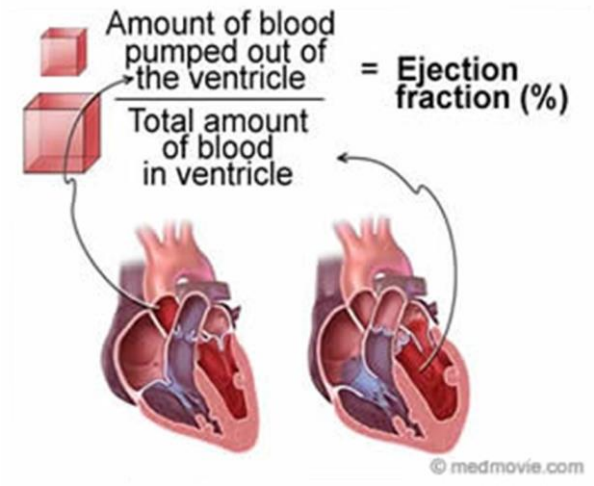
Mechanism of action& bebecicial effects of gliflozins in HF



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)

EF < 40%

Assessment of volume status

Signs and symptoms of fluid retention

Diuretic

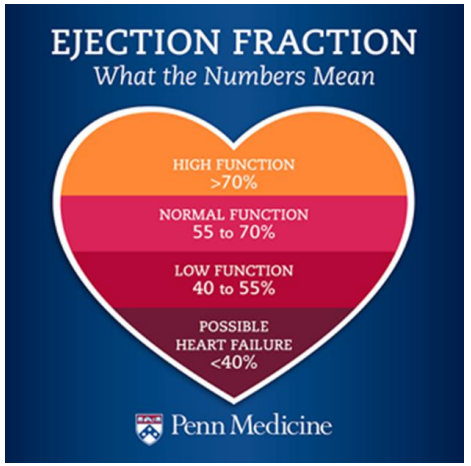
± digoxin

No signs and symptoms of fluid retention

ACE Inhibitor

β-blocker

Digoxin



References

Lippincott's Illustrated Review

Pharmacology, 8th edition

Lippincott Williams & Wilkins

Katzung *by Anthony Trevor, Bertram Katzung, and Susan Masters . 16th edition McGraw Hill,*

Rang & Dale's Pharmacology: *by Humphrey P. Rang ; James M. Ritter ; Rod Flower Churchill Livingstone; 10th edition*

Thank you