

# **Drug Therapy Of Heart Failure**

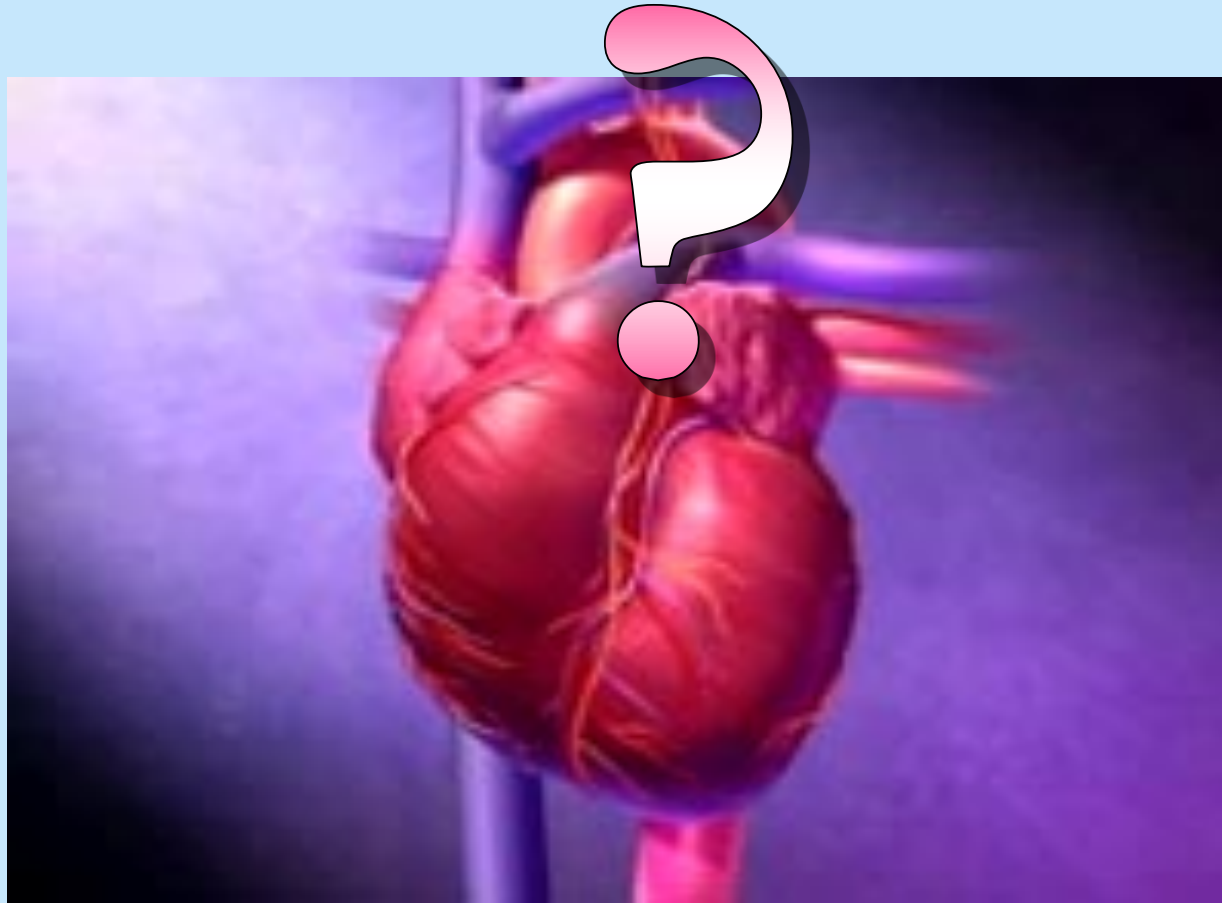
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# Learning objectives

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

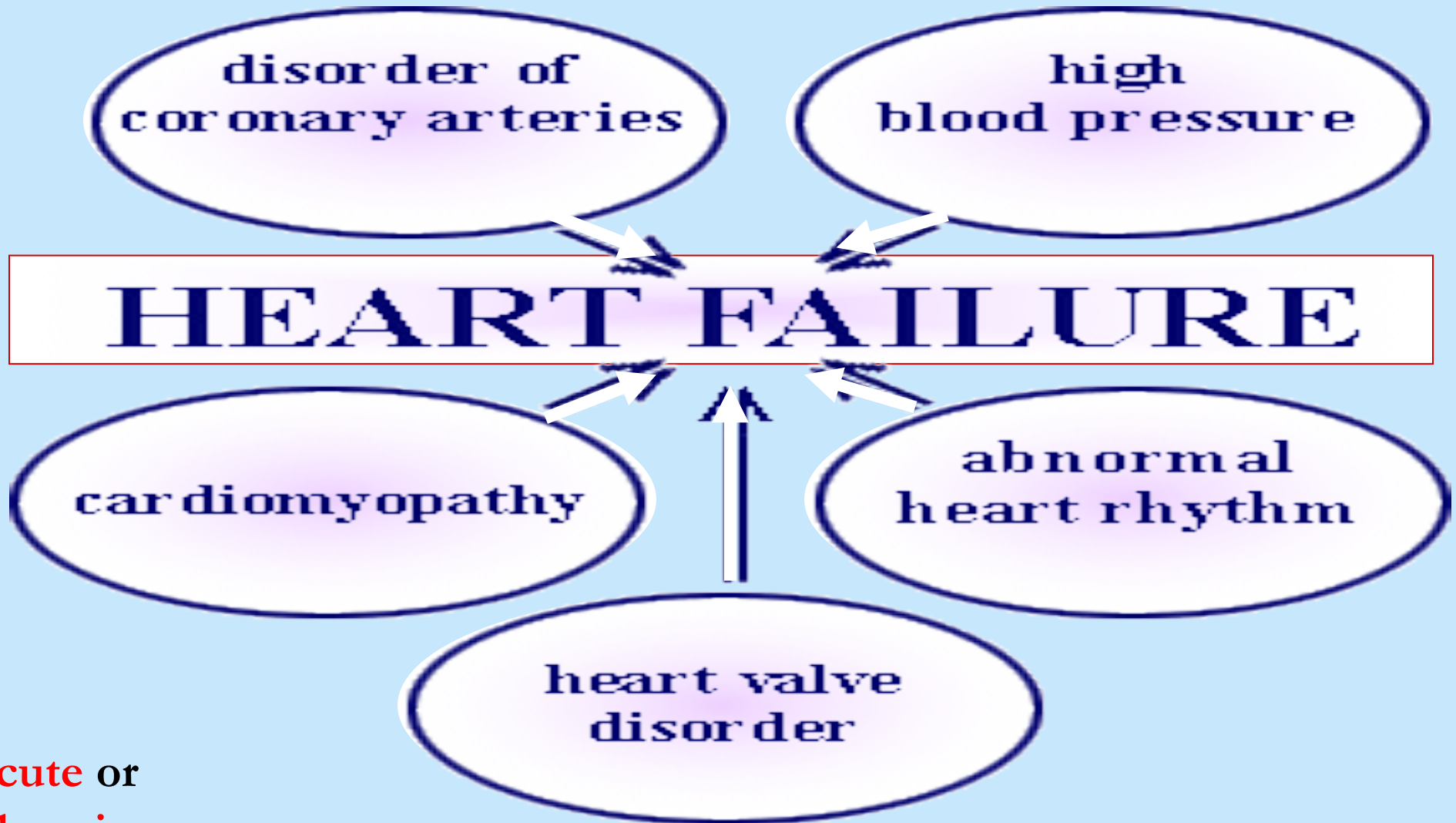
- **Describe** the different **classes of drugs** used for treatment of acute & chronic heart failure & their mechanism of action
- **Understand** their pharmacological effects, clinical uses, adverse effects & their interactions with other drugs.

# HEART FAILURE



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

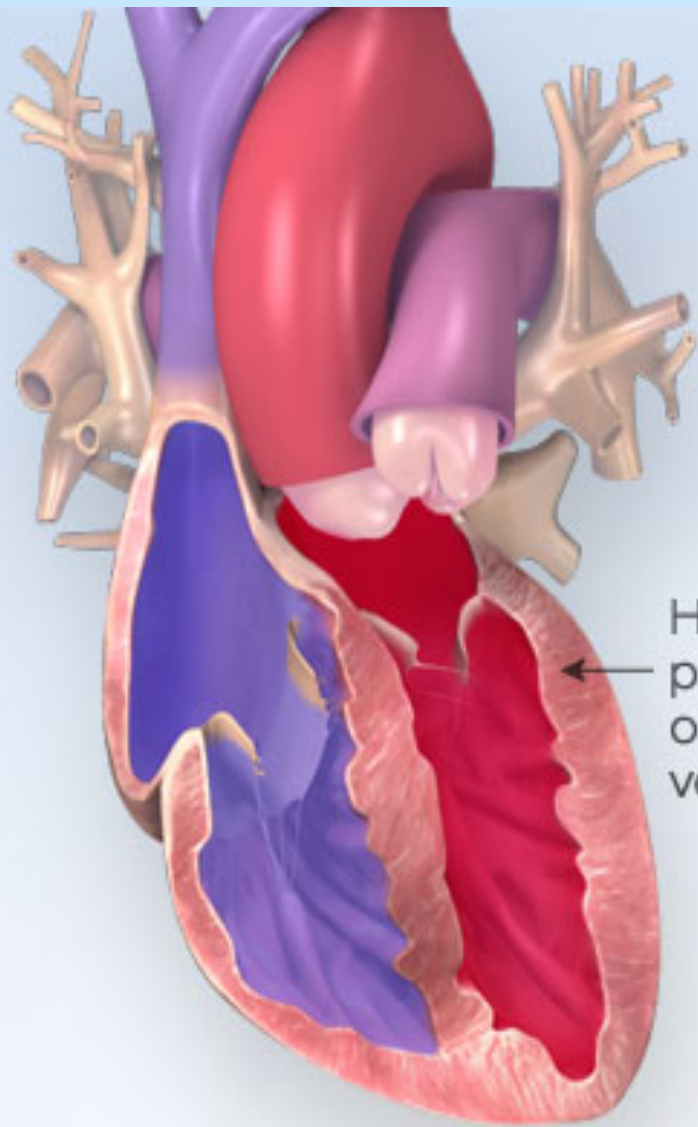
# CAUSES OF HEART FAILURE



**Acute** or  
**Chronic**

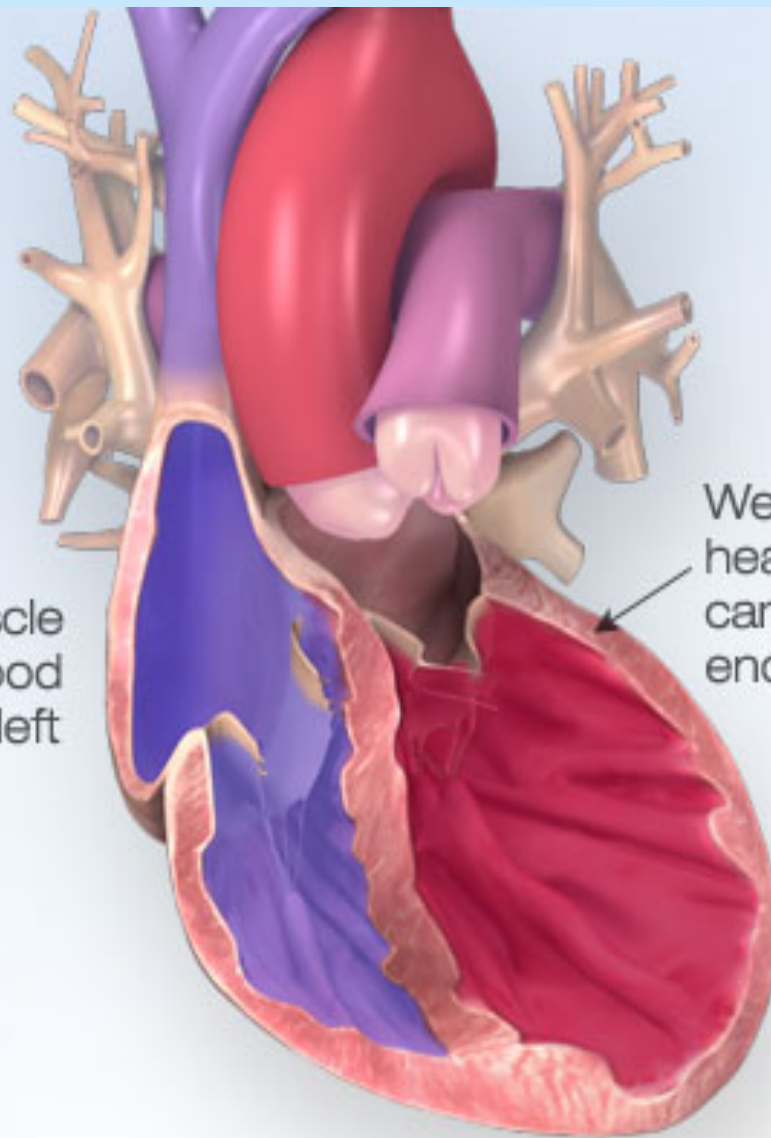
# Symptoms of Heart failure

- **Tachycardia**
- **Decreased exercise tolerance (rapid fatigue)**
- **Dyspnea (pulmonary congestion)**
- **Peripheral edema**
- **Cardiomegaly.**



Heart muscle pumps blood out of the left ventricle.

**Normal Heart**



Weakened heart muscle cannot pump enough blood.

**Heart Failure**

# Pathophysiology of CHF

↓ Force of contraction

↓  
**Low C.O.**

↓ Renal blood flow

↓ Carotid sinus firing

**Activate renin-angiotensin-  
Aldosterone system**

**Activate sympathetic system  
↑ Sympathetic discharge**

ALDOST.

Ag. II

**Remodeling**

Salt & Water  
Retention

Volume expansion

**Vasoconstriction**

Venous VC

Arterial VC

↑ Force of  
Cardiac .cont.

↑ HR

**↑ Preload**

**↑ Preload**

**↑ Afterload**

# Factors affecting cardiac output and heart failure

**1- Preload**

**2- Afterload**

**3- Cardiac contractility**



# Drugs used in treatment of heart failure

## I- Drugs that decrease preload:

- 1 - Diuretics
- 2 - Aldosterone antagonists
- 3 - Venodilators

## II- Drugs that decrease afterload:

- 1 - Arteriodilators

# Drugs used in treatment of heart failure

## III- Drugs that decrease both preload & afterload: (Combined arteriolo- & venodilators)

- 1- Angiotensin converting enzyme (ACE) inhibitors
- 2- Angiotensin receptor antagonists
- 3-  $\alpha_1$ -adrenoceptor antagonists
- 4- Direct vasodilators

# Drugs used in treatment of heart failure

## IV- Drugs that increase heart contractility:

- 1- **Cardiac glycosides (digitalis)**
- 2-  **$\beta$ - adrenoceptor agonists**
- 3- **Phosphodiesterase inhibitors**

# I- Drugs that decrease preload

## 1-Diuretics:

### Mechanism of action in heart failure :

reduce salt and water retention



decrease ventricular preload and venous pressure



reduction of cardiac size



Improvement of cardiac performance

# I- Drugs that decrease preload

## 1-Diuretics:

### **Chlorothiazide**

- first-line agent in heart failure therapy
- used in volume overload (pulmonary and/ or peripheral edema)
- used in mild congestive heart failure.

# I- Drugs that decrease preload

## 1-Diuretics:

### **Furosemide**

- a potent diuretic
- used for immediate reduction of pulmonary congestion & severe edema associated with :
  - acute heart failure
  - moderate & severe chronic failure

# I- Drugs that decrease preload

## 2-Aldosterone antagonists:

### **Spironolactone**

- non-selective antagonist of aldosterone receptor
- a potassium sparing diuretic
- improves survival in advanced heart failure

# I- Drugs that decrease preload

## 2-Aldosterone antagonists:

### Eplerenone

- a new selective aldosterone receptor antagonist

(does not inhibit other hormones such as estrogens & androgens)

- indicated to improve survival of stable patients with congestive heart failure.



# I- Drugs that decrease preload

## 3-Venodilators:

**A- Nitroglycerine**

**B- Isosorbide dinitrate**

- used I.V. for **severe** heart failure when the main symptom is dyspnea due to pulmonary congestion
- dilates venous blood vessels & reduce preload.

# II- Drugs that decrease afterload

## 1- Arteriodilators:

### Hydralazine

- used when the main symptom is rapid fatigue due to low cardiac output
- reduce peripheral vascular resistance

# **III- Drugs that decrease both preload & afterload**

## **1-Angiotensin converting enzyme (ACE) inhibitors:**

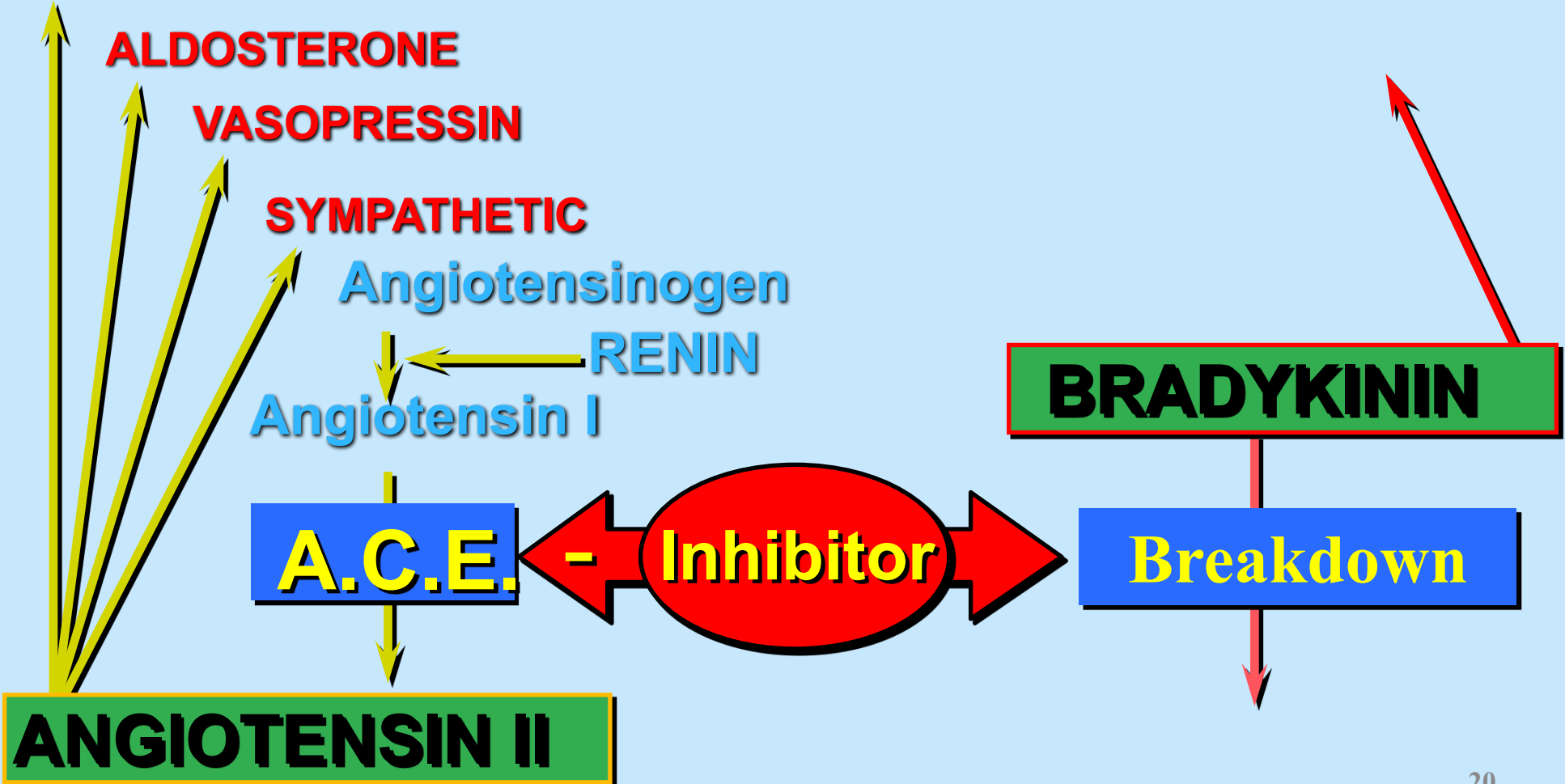
- considered as first-line drugs for chronic heart failure along with diuretics**
- first-line drugs for hypertension therapy.**

# Angiotensin converting enzyme inhibitors

## MECHANISM OF ACTION

**VASOCONSTRICTION**

**VASODILATATION**



# ACE Inhibitors

## Pharmacological actions:

- 1 - Decrease peripheral resistance (Afterload)
- 2 - Decrease Venous return (Preload)
- 3 - Decrease sympathetic activity
- 4- Inhibit cardiac and vascular remodeling  
associated with chronic heart failure



**Decrease in mortality rate**

# ACE Inhibitors

## Captopril, Enalapril and Ramipril

### Pharmacokinetics:

- rapidly absorbed from GIT after oral administration
- food reduce their bioavailability

## Enalapril , Ramipril

- prodrugs, converted to their active metabolites in liver
- have long half-life & given once daily.

# ACE Inhibitors

## Adverse effects:

- 1- acute renal failure, especially in patients with renal artery stenosis
- 2- hyperkalemia, especially in patients with renal insufficiency or diabetes
- 3- severe hypotension in hypovolemic patients (due to diuretics, salt restriction or gastrointestinal fluid loss).

# ACE Inhibitors

## Adverse effects:

**4- dry cough sometimes with wheezing**

**5- angioneurotic edema (swelling in the  
nose, throat, tongue, larynx)**

**6- dysgeusia (reversible loss or altered taste).**



# ACE Inhibitors

## Contraindications:

- during the second & third trimesters of pregnancy  
(due to the risk of : fetal hypotension, renal failure & malformations)
- renal artery stenosis.

### **III- Drugs that decrease both preload & afterload**

#### **2- Angiotensin receptor blockers (ARBs) :**

**Losartan, Valsartan, Irbesartan**

#### **Mechanism of action:**

- block AT<sub>1</sub> receptors**
- decrease action of angiotensin II**

## **III- Drugs that decrease both preload & afterload**

### **3- $\alpha$ -ADRENOCEPTOR BLOCKERS :**

#### **Prazosin**

- blocks  $\alpha$ - receptors in arterioles and venules**
- decrease both afterload & preload**

### III- Drugs that decrease both preload & afterload

#### 4- **Direct** acting vasodilators:

#### **Sodium nitroprusside**

- given I.V. for acute or **severe** heart failure
- acts immediately and effects lasts for 1-5 min.

# IV- Drugs that increase contractility

## 1- Cardiac glycosides (digitalis) :

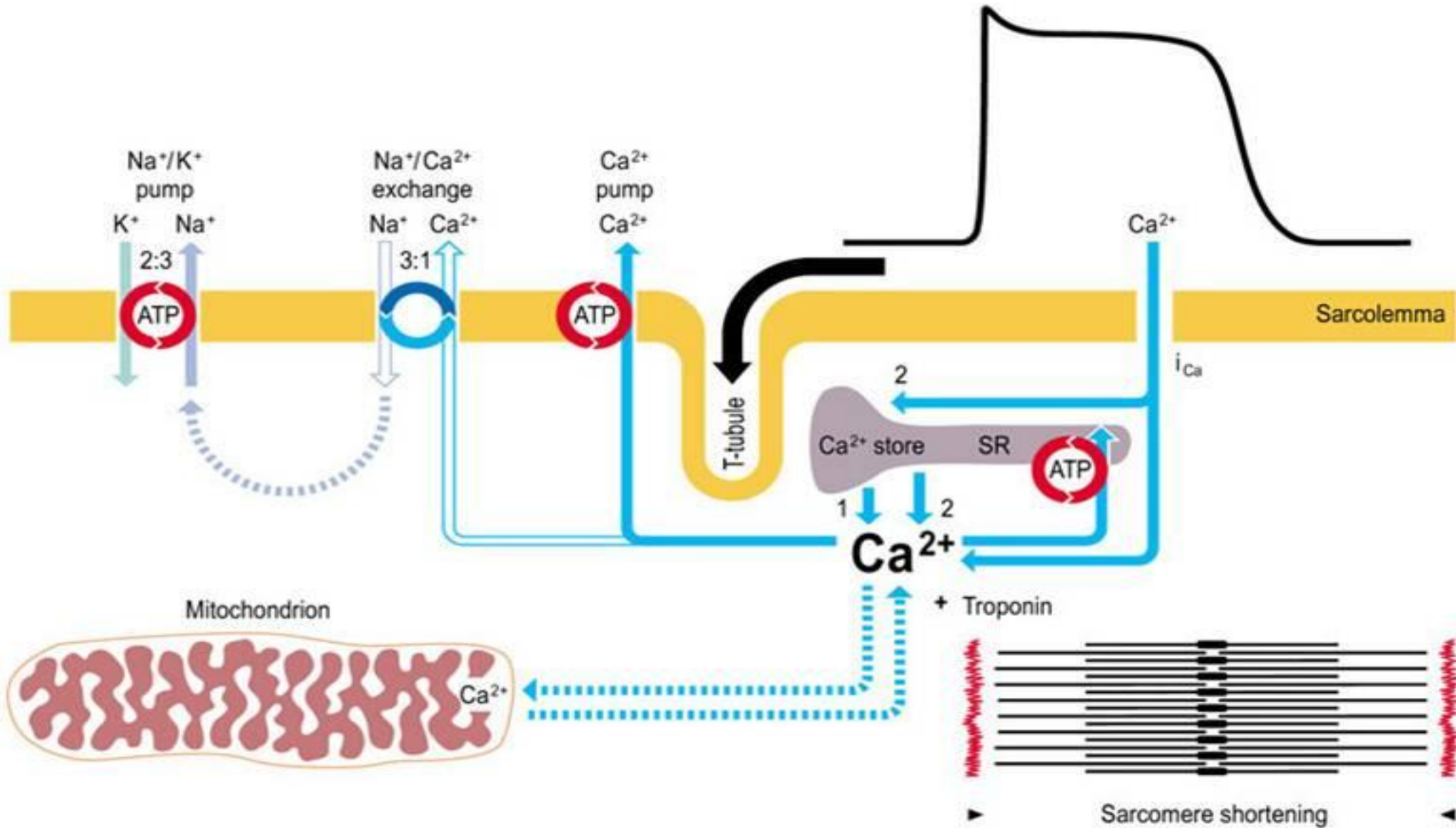
### Digoxin

- increases the force of myocardial contraction  
(+ve inotropic effect)

### Mechanism of action :

- Inhibit  $\text{Na}^+ / \text{K}^+$  ATPase enzyme  
(the sodium pump)

# MECHANISM OF ACTION OF DIGOXIN



## IV- Drugs that increase contractility

### 1- Cardiac glycosides (digitalis) :

**Digoxin**

#### Therapeutic uses:

- Congestive heart failure
- has narrow therapeutic index

## IV- Drugs that increase contractility

### 1- Cardiac glycosides (digitalis) :

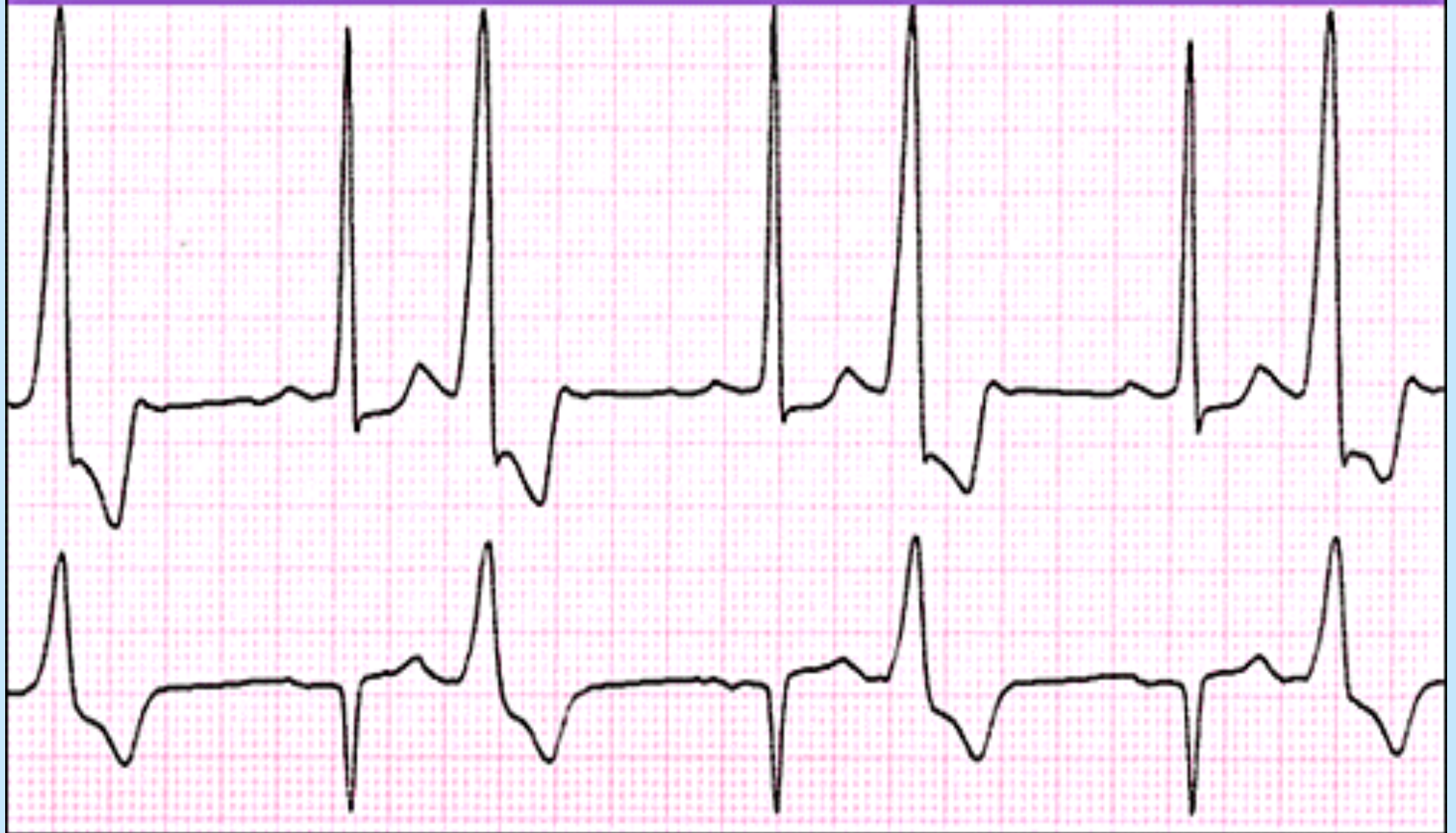
**Digoxin**

#### Adverse effects (Cardiac):

- digitalis-induced arrhythmias
  - extrasystoles
  - coupled beats (**Bigeminal rhythm**)
  - ventricular tachycardia or fibrillation
  - cardiac arrest



## Bigeminal PVC's: every other beat is a PVC.



## **IV- Drugs that increase contractility**

### **1- Cardiac glycosides (digitalis):**

#### **Digoxin**

#### **Adverse effects (non-cardiac):**

#### **GIT:**

**anorexia, nausea, vomiting, diarrhea**

#### **CNS:**

**headache, visual disturbances, drowsiness.**

# IV- Drugs that increase contractility

## 1- Cardiac glycosides (digitalis) :

### **Digoxin**

#### Factors that increase its toxicity:

- Renal diseases
- Hypokalemia
- Hypomagnesemia
- Hypercalcemia

## IV- Drugs that increase contractility

### 2- $\beta$ -Adrenoceptor agonists:

#### **Dobutamine**

- **Selective  $\beta_1$  agonist**
- **Uses : Treatment of acute heart failure in cardiogenic shock**

## IV- Drugs that increase contractility

### 3- phosphodiesterase -III inhibitors:

**Milrinone**

#### Mechanism of action:

- Inhibits phosphodiesterase -III (cardiac & B. Vessels)



**Increase** cardiac  
Contractility



**dilatation** of arteries & veins  
(reduction of preload & afterload)

## IV- Drugs that increase contractility

### 3- phosphodiesterase -III inhibitors :

**Milrinone**

#### Therapeutic 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

## IV- Drugs that increase contractility

### 3- phosphodiesterase -III inhibitors :

#### **Milrinone**

#### Adverse effects:

- Hypotension and chest pain (angina)

#### Chemical interaction:

- furosemide should not be administered in I.V. lines containing milrinone due to formation of a precipitate

- **Enoximone & Vesnarinone**  
new drugs in clinical trials.

# The use of $\beta$ -adrenoceptor blockers in heart failure

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

## $\beta$ -blockers:

- reduce the progression of chronic heart failure
- **not** used in acute heart failure.



# The use of $\beta$ -adrenoceptor blockers in heart failure

## Mechanism of action of $\beta$ -blockers in HF:

- 1- attenuate cardiac remodeling
- 2- slow heart rate, which allows the left ventricle  
to fill more completely
- 3- decrease renin release



**reduce mortality & morbidity of patients with HF**

# The use of $\beta$ -adrenoceptor blockers in heart failure

## - Second generation:

cardioselective ( $\beta_1$ -receptors)

e.g. **Bisoprolol, Metoprolol**

## - Third generation:

$\beta_1$ -receptors blocker & have vasodilator actions  
( $\alpha$ - blocking effect)

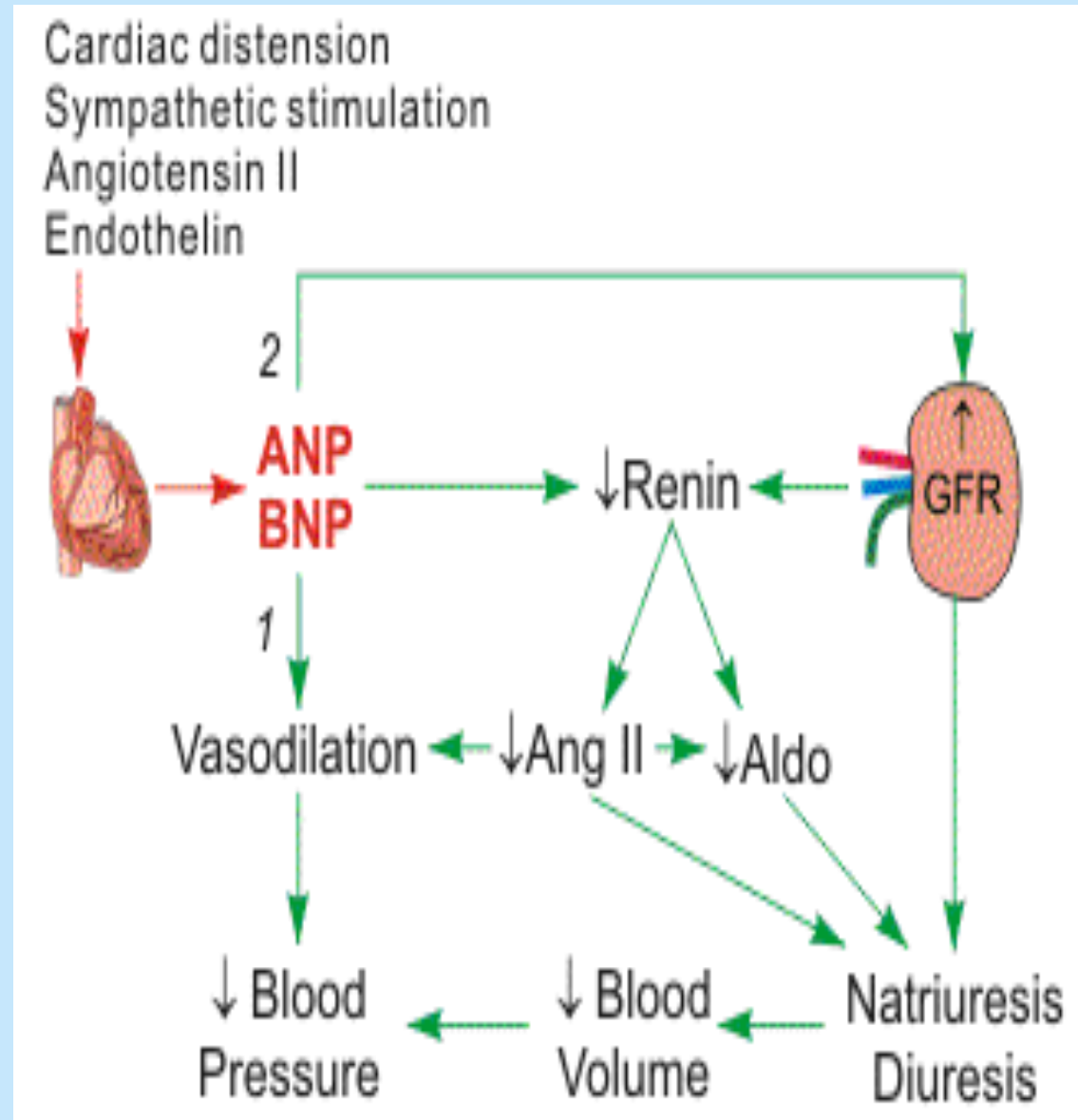
e.g. **Carvedilol , Nebivolol.**

# New drugs for heart failure

## 1- Natriuretic Peptides:

### Nesiritide

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



# Natriuretic Peptides

## Nesiritide

- a purified preparation of human BNP, manufactured by recombinant DNA technology
- ↑ cyclic-GMP in vascular smooth muscle, leading to smooth muscle relaxation & reduction of preload and afterload
- indicated (IV) for the treatment of patients with acute decompensated heart failure (ADHF) who have dyspnea at rest or with minimal activity.

# New drugs for heart failure

## 2- Calcium sensitisers:

### **Levosimendan**

- **used in the management of ADHF**

# New drugs for heart failure

## Levosimendan

### mechanism of action:

- **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.**

# Management of chronic heart failure

- **Reduce work load of the heart**
  - **Limit patient activity**
  - **Reduce weight**
  - **Control hypertension**
- **Restrict sodium**
- **Stop smoking.**

# Heart Failure Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but <b>no symptoms &amp; no limitation</b> in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc
II	Mild symptoms ( <b>mild</b> shortness of breath &/or angina), <b>slight</b> limitation during ordinary activity
III	<b>Marked</b> limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest
IV	<b>Severe</b> limitations. Experiences symptoms even while at rest. Mostly bedbound patients.



# Management of chronic heart failure

	For Survival/Morbidity	For Symptoms
NYHA I	Continue ACE inhibitor/ARB if ACE inhibitor intolerant, continue aldosterone antagonist if post-MI add beta-blocker if post-MI	reduce / stop diuretic
NYHA II	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
NYHA III	ACE inhibitor plus ARB or ARB alone if ACE intolerant beta-blocker add aldosterone antagonist	+ diuretics + digitalis If still symptomatic
NYHA IV	Continue ACE inhibitor/ARB beta-blocker Aldosterone antagonist	+diuretics + digitalis + consider temporary inotropic support

# Congestive Heart Failure in Black patients

## Hydralazine/isosorbide dinitrate fixed dose combination

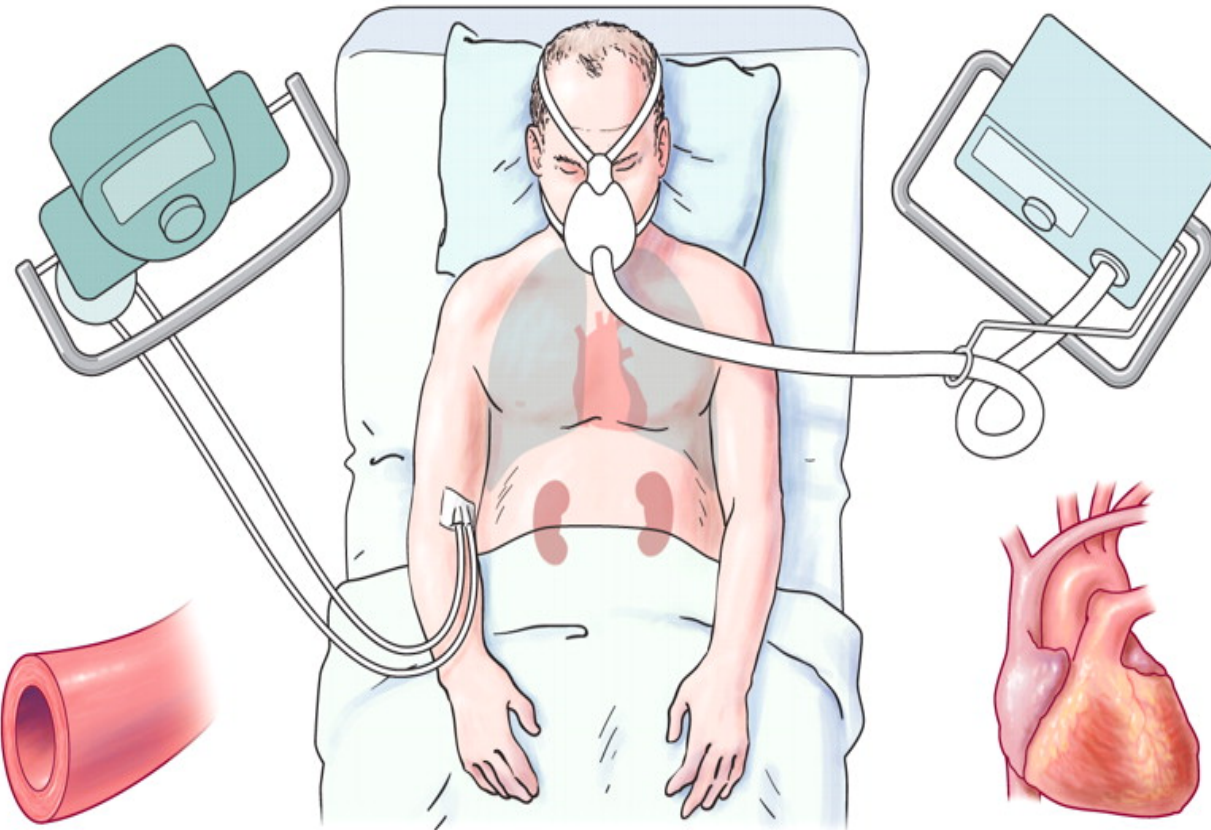
- FDA approved to add to standard therapy for black Americans with congestive heart failure  
  
(due to poor response to ACE inhibitors)
- should be considered for patients intolerant to ACE inhibitors & ARBs due to  
  
renal dysfunction

# 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.**

# Management of acute heart failure



Ultrafiltration:  
*Aqua/natriuresis*

Bilevel or continuous  
positive airway pressure:  
*Preload reduction*

Nitrates, nitroprusside,  
dobutamine:  
*Arterial vasodilation*

Dobutamine,  
dopamine, milrinone:  
*Increased inotropy*

Nitrates, morphine:  
*Venodilation*

Furosemide:  
*Natriuresis*

**Thank you**

