

Heart Failure (HF) Treatment

Heart Failure (HF)

- Complex, progressive disorder.
- The heart is unable to pump sufficient blood to meet the needs of the body.
- Its cardinal symptoms are **dyspnea**, **fatigue**, and **fluid retention**.
- **Impaired** ability of the heart to adequately **fill** with and/or **eject** blood.
- It is often accompanied by **abnormal increases** in **blood volume** and **interstitial fluid**.
- ✓ Underlying causes of HF include arteriosclerotic heart disease, myocardial infarction, hypertensive heart disease, valvular heart disease, and congenital heart disease.

Compensatory Mechanisms in the Progression of HF

- Chronic activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system is associated with:
 - **Remodeling of Cardiac Tissue.**
 - **Loss of Myocytes.**
 - **Hypertrophy.**
 - **Fibrosis.**
- This Prompts additional neurohormonal activation.
- If left untreated, leads to death.

Goals of Pharmacologic Intervention in HF

- ✓ **Alleviate Symptoms.**
- ✓ **Slow Disease Progression.**
- ✓ **Improve Survival.**

□ **Seven Classes of Drugs:**

- 1) **Angiotensin-converting Enzyme Inhibitors.**
- 2) **Angiotensin-receptor Blockers.**
- 3) **Aldosterone antagonists,**
- 4) **β-blockers.**
- 5) **Diuretics.**
- 6) **Direct Vaso- and Venodilators.**
- 7) **Inotropic agents.**

- **Depending on the severity of HF individual patient factors, one or more of these classes of drugs are administered.**

Drugs of HF treatment

ACE INHIBITORS

Captopril CAPOTEN
Enalapril VASOTEC
Fosinopril MONOPRIL
Lisinopril PRINIVIL, ZESTRIL
Quinapril ACCUPRIL
Ramipril ALTACE

ANGIOTENSIN RECEPTOR BLOCKERS

Candesartan ATACAND
Losartan COZAAR
Telmisartan MICARDIS
Valsartan DIOVAN

ALDOSTERONE ANTAGONISTS

Eplerenone INSPRA
Spironolactone ALDACTONE

β-ADRENORECEPTOR BLOCKERS

Bisoprolol ZEBETA
Carvedilol COREG, COREG CR
Metoprolol succinate TOPROL XL
Metoprolol tartrate LOPRESSOR

DIURETICS

Bumetanide BUMEX
Furosemide LASIX
Metolazone ZAROXOLYN
Torsemide DEMADEx

DIRECT VASO - AND VENODILATORS

Hydralazine APRESOLINE
Isosorbide dinitrate DILATRATE-SR,
ISORDIL
FDC Hydralazine/Isosorbide dinitrate
BIDIL

INOTROPIC AGENTS

Digoxin LANOXIN
Dobutamine DOBUTREX
Milrinone PRIMACOR

Pharmacologic Intervention Provides the Following Benefits

- Reduced Myocardial Work Load.
- Decreased Extracellular Fluid Volume.
- Improved Cardiac Contractility.
- A Reduced rate of cardiac remodeling.

Therapeutic strategies in HF

- Chronic HF is typically managed by **fluid limitations** (less than 1.5 to 2 L daily).
- Low dietary intake of **sodium** (less than 2000 mg/d).
- Treatment of comorbid conditions.
- Use of diuretics.
- Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, nondihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be avoided if possible.
- Inhibitors of the renin–angiotensin–aldosterone system, and inhibitors of the sympathetic nervous system.
- **Inotropic agents** are reserved for acute HF signs and symptoms in mostly the **inpatient** setting.

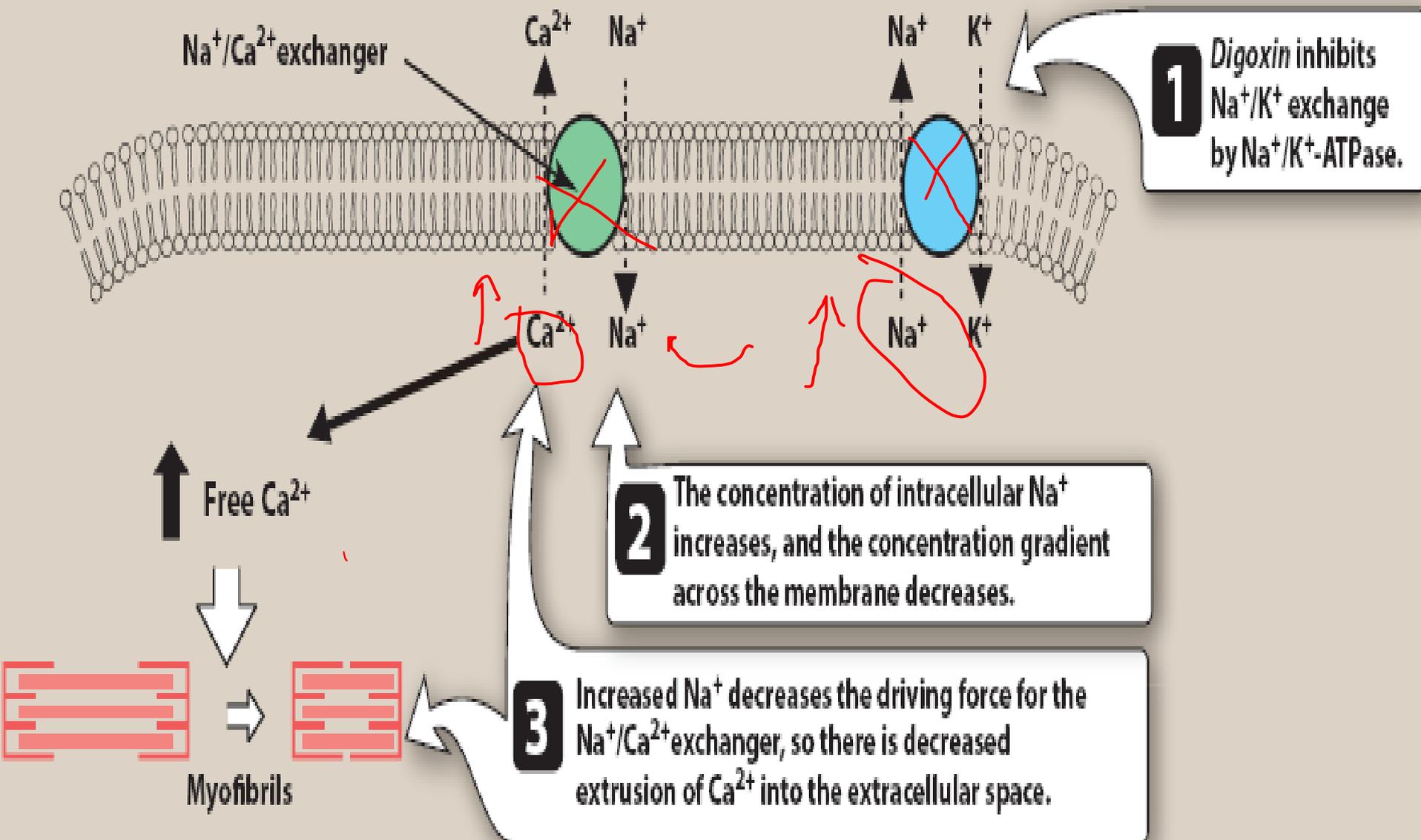
Inotropic Drugs

- HF with reduced ejection fraction (HFrEF)
- Positive inotropic agents enhance cardiac contractility and, thus increase cardiac output.
- Although these drugs act by different mechanisms the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.
- All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival.
- For this reason, these agents, with the exception of digoxin, are only used for a short period mainly in the inpatient setting.

Digitalis glycosides

- The **cardiac glycosides** are often called **digitalis** or **digitalis glycosides** because most of the drugs come from the digitalis (foxglove) plant.
- **Increase the contractility** of the heart muscle and, therefore, are used in treating HF.
- The digitalis glycosides have **a low therapeutic index**. with only a small difference between a therapeutic dose and doses that are toxic or even fatal. The most widely used agent is **digoxin**.

Mechanism of Action



- ✓ Digoxin increases the force of **cardiac contraction**, causing **cardiac output** to more closely resemble that of the normal heart
- ✓ **Vagal tone** is also enhanced, so both heart rate and myocardial oxygen demand decrease.
- ✓ Digoxin slows **conduction** velocity through the **AV node**, making it useful for atrial fibrillation.

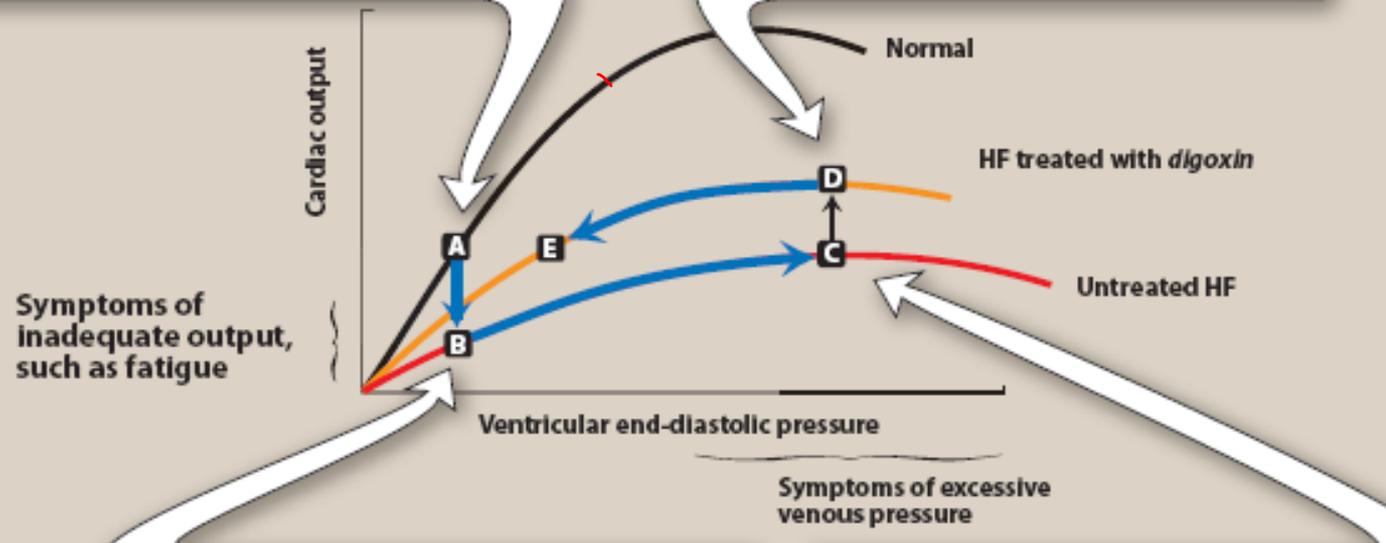
- low-dose digoxin **inhibits sympathetic** activation with minimal effects on contractility.
- This effect is the reason a **lower serum drug** concentration is targeted in HFrEF.
- When $\text{Na}^+/\text{K}^+-\text{ATPase}$ is markedly inhibited by digoxin, the resting **membrane potential** may increase (-70 mV instead of -90 mV), which makes the membrane more excitable, increasing the risk of arrhythmias (**toxicity**).

1 NORMAL HEART

- Within limits, when cardiac muscle is stretched, its force of contraction increases and, hence, cardiac output increases.
- However, if the ventricle is overly stretched, the effect of ventricular contraction is diminished.
- **A** is the normal operating point in the healthy heart.

4 DIGOXIN TREATMENT

- Administration of *digoxin* at doses that cause positive inotropy shifts the ventricular function curve toward normal.
- Increased contractility (**C** to **D**) leads to increased cardiac output.
- Decreased sympathetic reflexes and vascular tone cause a decrease in the ventricular end-diastolic pressure (**D** to **E**).



2 DECOMPENSATED HEART FAILURE

- Initial reduction of contractility (**A** to **B**) due to HF.
- Symptoms of low cardiac output develop—for example, fatigue.

3 COMPENSATED HEART FAILURE

- Ventricular end-diastolic pressure increases (**B** to **C**) in an effort to maintain an adequate cardiac output.
- The increased ventricular end-diastolic pressure causes symptoms of congestion—for example, dyspnea.

- Digoxin therapy is indicated in patients with **severe** HFrEF after initiation of ACE inhibitor, β -blocker, and diuretic therapy.
- A low serum drug concentration of digoxin (0.5 to 0.8 ng/mL) is beneficial in HFrEF.
- At this level, patients may see a reduction in HF admissions, along with improved survival.
- At higher serum drug concentrations, admissions are prevented, but **mortality likely increases**.
- Digoxin is not indicated in patients with diastolic or right sided HF unless the patient has concomitant atrial fibrillation or flutter.
- **Patients with mild to moderate HF often respond to treatment with ACE inhibitors, β -blockers, aldosterone antagonists, direct vaso- and venodilators, and diuretics and may **not require digoxin**.**

Pharmacokinetics

- **Digoxin** is available in **oral** and **injectable formulations**.
- It has a large volume of distribution, because it accumulates in muscle.
- In acute situations such as symptomatic atrial fibrillation, a loading dose regimen is used.
- Digoxin has a **long half-life** of 30 to 40 hours.
- It is mainly eliminated intact by the **kidney**, requiring dose adjustment in **renal dysfunction**.

Adverse Effects

- At **low** serum drug concentrations, digoxin is fairly well **tolerated**.
- It has a **very narrow therapeutic index**, and **digoxin toxicity** is one of the most common adverse drug reactions leading to hospitalization.
- **Anorexia, nausea, and vomiting** may be initial indicators of toxicity. Patients may also experience blurred vision, and various cardiac arrhythmias.
- Toxicity can often be managed by **discontinuing digoxin**,

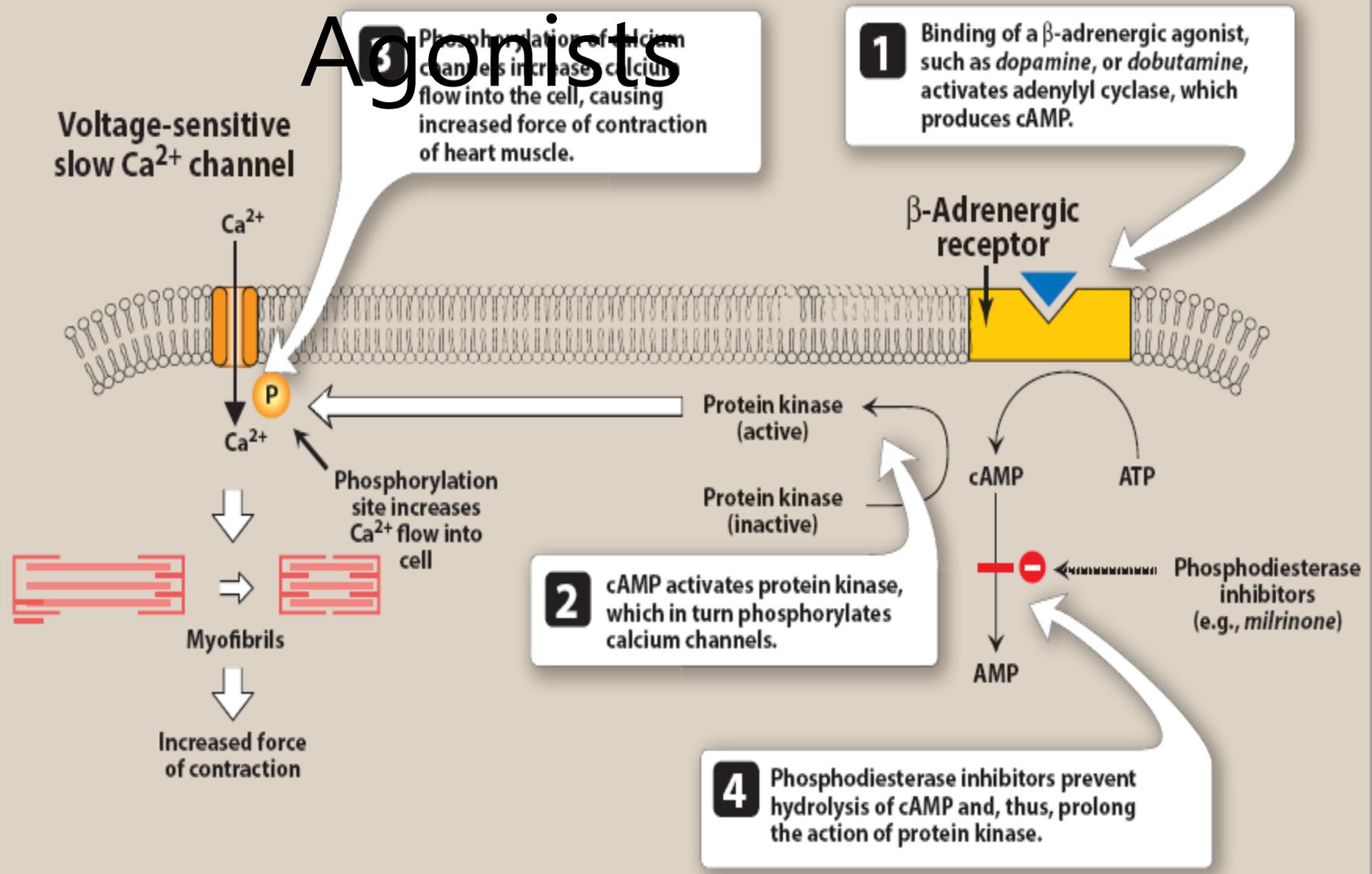
- Determining serum potassium levels, and, if indicated, replacing potassium.
- Decreased levels of serum potassium (**hypokalemia**) predispose a patient to **digoxin toxicity**, since digoxin normally **competes with potassium for the same binding site** on the Na⁺/K⁺-ATPase pump.
- Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic

- With the use of a **lower serum drug concentration** in HFrEF, toxic levels are **infrequent**.
- Clarithromycin, Verapamil, and Amiodarone, can significantly **increase digoxin levels**, necessitating a reduced dose of digoxin.
- Digoxin should also be used with caution with other drugs that **slow AV** conduction, such as β -blockers, verapamil, and diltiazem.

β -Adrenergic agonists

- **Dobutamine.**
- **Dopamine** improve cardiac performance by causing positive inotropic effects and vasodilation.
- ✓ **Dobutamine** is the most commonly used **inotropic agent** other than digoxin.
- β -Adrenergic agonists lead to an increase in intracellular cyclic adenosine monophosphate (cAMP), which results in the activation of protein kinase. Protein kinase then phosphorylates slow calcium channels, thereby increasing entry of calcium ions into the myocardial cells and enhancing contraction.
- Both drugs must be given by **intravenous infusion** and are primarily used in the **short-term treatment of acute HF** in the hospital setting.

β-Adrenergic Agonists



Phosphodiesterase inhibitors

- **Milrinone**
- a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP.
- Like β -adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility.
- **Long-term**, milrinone therapy may be associated with a substantial increased risk of mortality.
- **Short-term** use of intravenous milrinone is not associated with increased mortality in patients without a history of coronary artery disease, and some symptomatic benefit may be obtained in patients with refractory HF.

Vaso and Venodilator

- Dilation of **venous blood** vessels leads to a decrease in **cardiac preload**.
- **Nitrates** are commonly used venous dilators to reduce **preload** for patients with chronic HF.
- ✓ **Arterial** dilators, such as **hydralazine** reduce systemic arteriolar resistance and decrease **afterload**.
- If the patient is intolerant of **ACE inhibitors** or **β-blockers**, or if additional vasodilator response is required, a combination of **hydralazine** and **isosorbide** dinitrate may be used. A fixed-dose combination of these agents has been shown to improve symptoms and survival in black patients with HFrEF on standard HF treatment (β-blocker plus ACE inhibitor or ARB).
- ✓ Headache, hypotension, and tachycardia are **common adverse** effects with this combination.

β -blockers

- Evidence clearly demonstrates improved systolic functioning.
- Reverse cardiac remodeling in patients receiving β -blockers.
- Initial exacerbation of symptoms.
- The **benefit** of β -blockers is attributed, in part, to their ability to prevent the changes that occur because of chronic activation of the sympathetic nervous system.
- These agents decrease heart rate and inhibit **release of renin** in the kidneys.
- β -blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, **decreasing remodeling, hypertrophy,** and cell death.
- Three β -blockers have shown benefit in HF: **bisoprolol**, **carvedilol** and long-acting **metoprolol** succinate.
- ✓ Treatment should be started at low doses and gradually titrated to target doses

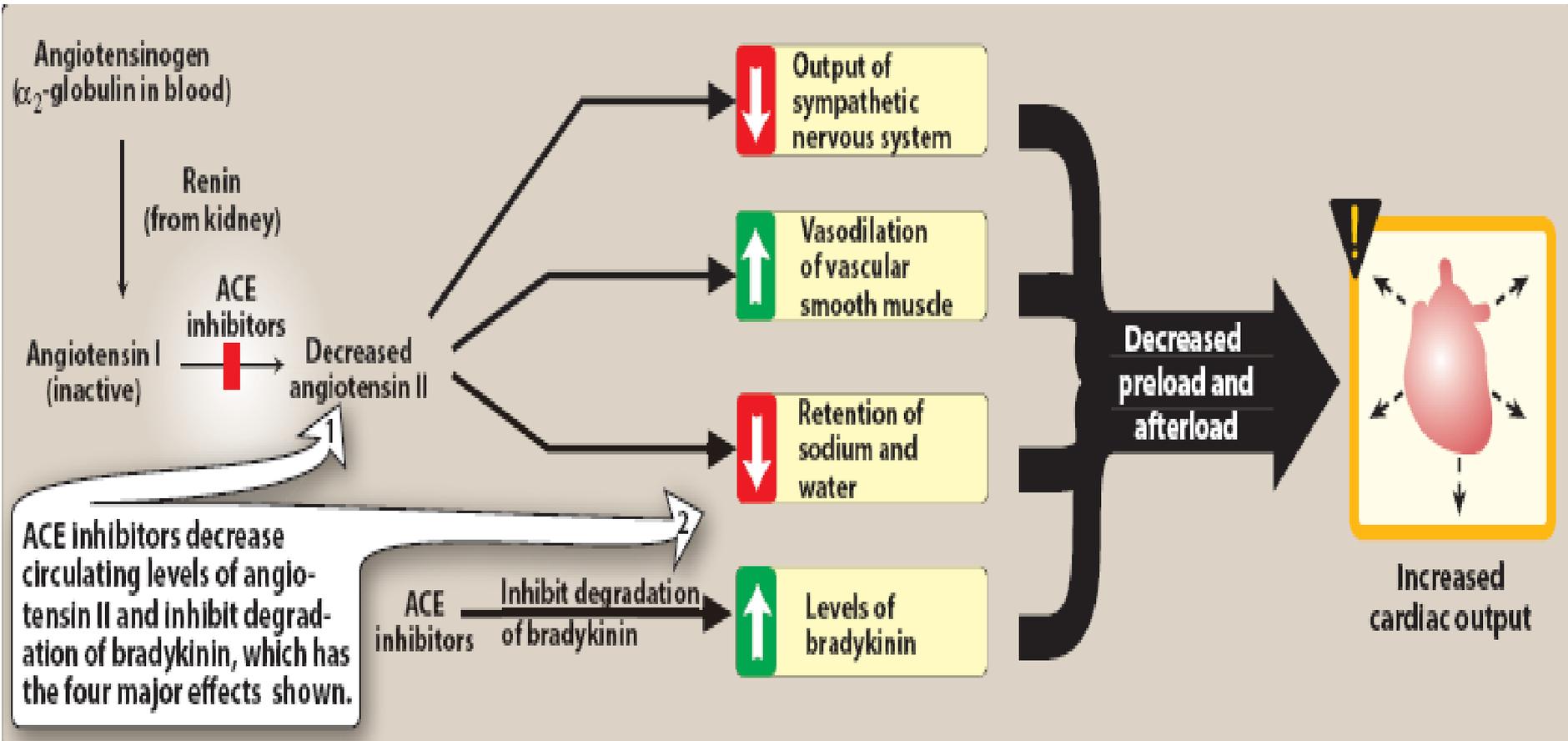
Diuretics

- Relieve **pulmonary** congestion and peripheral **edema**.
- These agents are also useful in reducing the symptoms of volume overload, including orthopnea and paroxysmal nocturnal **dyspnea**.
- Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (**preload**). This decreases cardiac workload and oxygen demand.
- Diuretics may also decrease **afterload** by reducing plasma volume, thereby decreasing blood pressure.
- **Loop diuretics** are the most commonly used diuretics in HF.
- These agents are used for patients who require **extensive diuresis** and those with renal insufficiency.

Aldosterone Antagonists

- Patients with advanced heart disease have elevated levels of **aldosterone** due to **angiotensin II** stimulation and reduced hepatic clearance of the hormone.
- **Spironolactone** is a direct antagonist of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia.
- **Eplerenone** is a competitive antagonist of aldosterone at mineralocorticoid receptors.
- Although similar in action to spironolactone at the mineralocorticoid receptor, **eplerenone** has a **lower incidence** of endocrine-related side effects due to its reduced affinity for glucocorticoid, androgen, and progesterone receptors.
- Aldosterone antagonists are indicated in patients with more severe stages.

- Angiotensin-converting enzyme inhibitors



Order of Therapy

