Heart Failure

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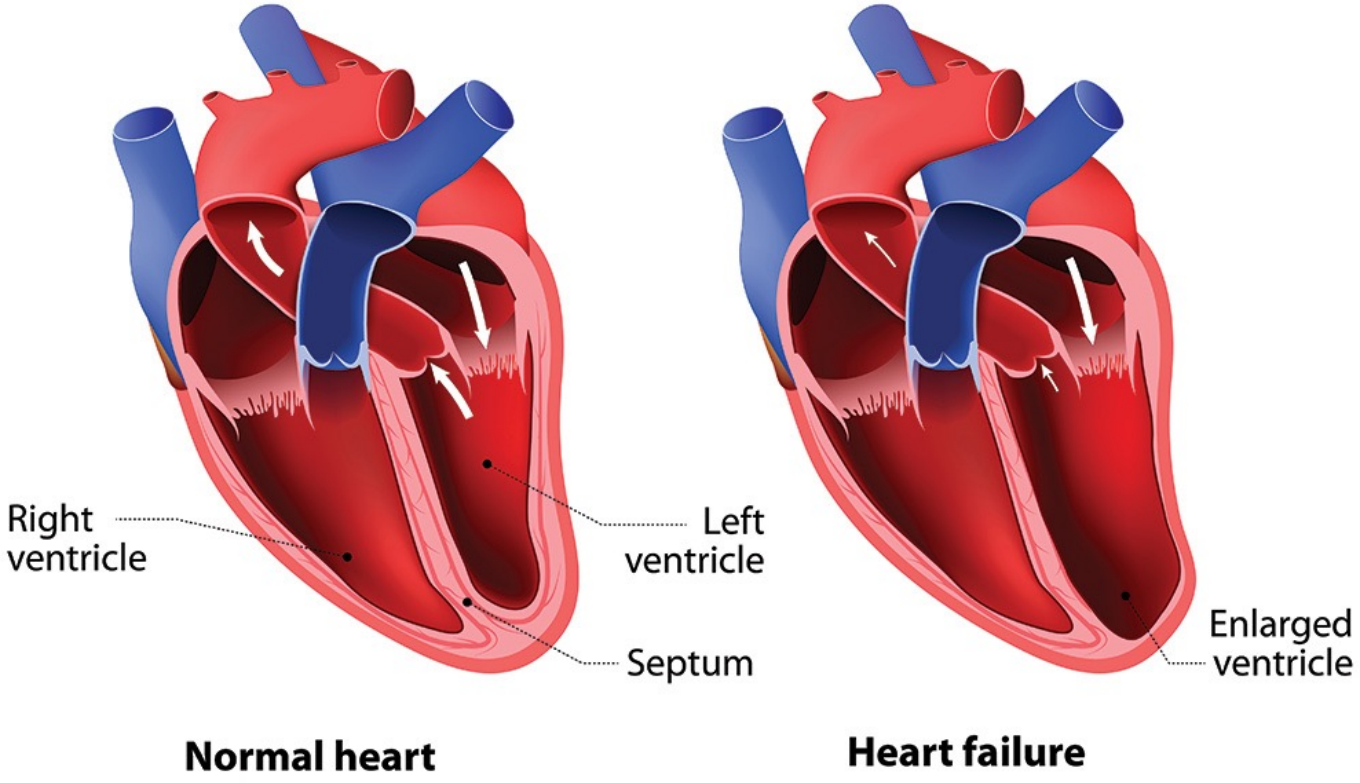


Heart failure

- Heart failure (HF) is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.

- Its cardinal symptoms are dyspnea, fatigue, and fluid retention.

- HF is due to an 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, dilated cardiomyopathy, and congenital heart disease.

Heart failure

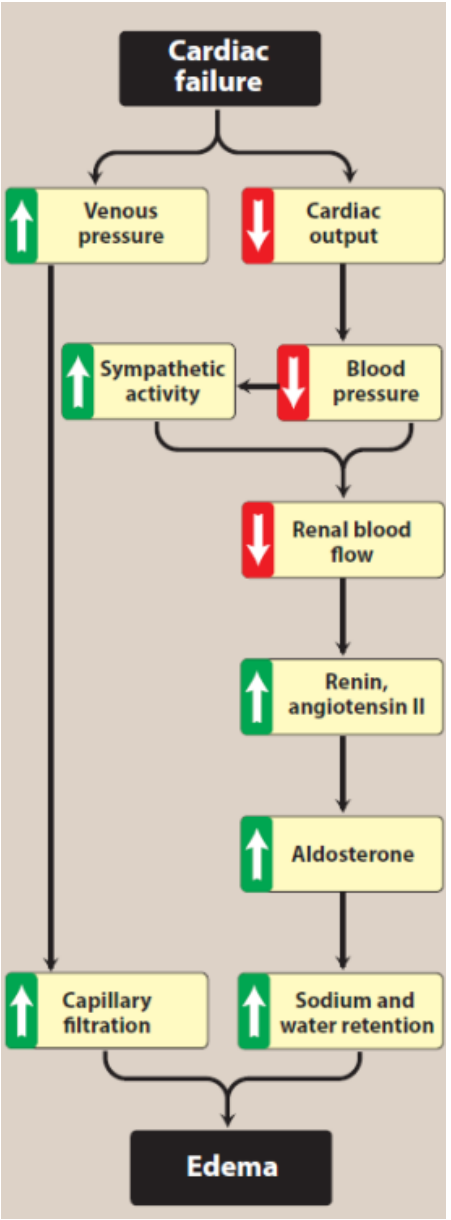
A. Role of physiologic compensatory mechanisms in the progression of HF

- Chronic activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system is associated with remodeling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis. This prompts additional neurohormonal activation, creating a vicious cycle that, if left untreated, leads to death.

B. Goals of pharmacologic intervention in HF

- Goals of treatment are to alleviate symptoms, slow disease progression, and improve survival. Accordingly, seven classes of drugs have been shown to be effective: **1) angiotensin-converting enzyme inhibitors, 2) angiotensin-receptor blockers, 3) aldosterone antagonists, 4) β-blockers, 5) diuretics, 6) direct vaso- and venodilators, and 7) inotropic agents**.

- Pharmacologic intervention provides the following benefits in HF: reduced myocardial workload, decreased extracellular fluid volume, improved cardiac contractility, and a reduced rate of cardiac remodeling.



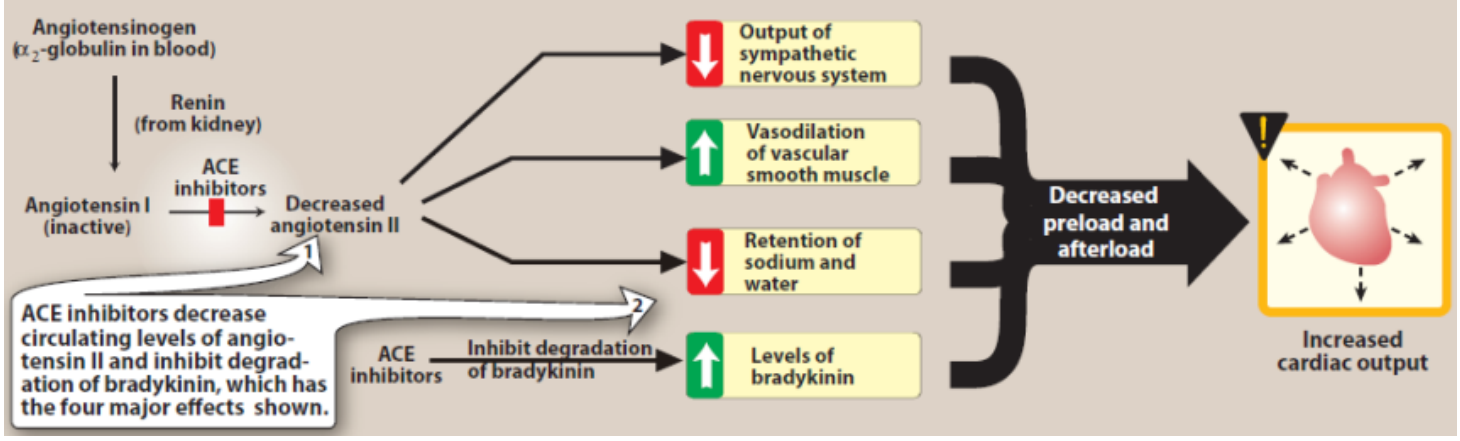
1. Inhibitors of the renin-angiotensin-aldosterone system

A. Angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril)

- ACE inhibitors are a part of standard pharmacotherapy in HFrEF. These drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. They also diminish the inactivation of bradykinin.
- Vasodilation occurs as a result of decreased levels of the vasoconstrictor angiotensin II and increased levels of bradykinin (a potent vasodilator). By reducing angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone.

Actions on the heart: ACE inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output. ACE inhibitors also blunt the usual angiotensin II–mediated increase in epinephrine and aldosterone seen in HF.

ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF.



1. Inhibitors of the renin-angiotensin-aldosterone system

Indications:

- ACE inhibitors may be considered for patients with asymptomatic and symptomatic heart failure with reduced ejection fraction (HFrEF).

- Importantly, ACE inhibitors are indicated for patients with all stages of left ventricular failure.

- Patients with the lowest ejection fraction show the greatest benefit from use of ACE inhibitors.

- Depending on the severity of HF, ACE inhibitors may be used in combination with diuretics, β-blockers, digoxin, aldosterone antagonists, and hydralazine/isosorbide dinitrate fixed-dose combination.

1. Inhibitors of the renin-angiotensin-aldosterone system

B. Angiotensin receptor blockers (ARBs) (candesartan, losartan, telmisartan, valsartan)

- ARBs are competitive antagonists of the angiotensin II type 1 receptor.

- ARBs have the advantage of more complete blockade of angiotensin II action, because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II. Further, ARBs do not affect bradykinin levels.

- Although ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical. Even so, ARBs are a substitute for ACE inhibitors in those patients who cannot tolerate the latter.

Actions on the cardiovascular system:

- Although ARBs have a different mechanism of action than ACE inhibitors, their actions on preload and afterload are similar.
- Their use in HF is mainly as a substitute for ACE inhibitors in those patients with severe cough or angioedema, which are thought to be mediated by elevated bradykinin levels.

1. Inhibitors of the renin-angiotensin-aldosterone system

C. Aldosterone antagonists (epleronone and spironolactone)

- 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 of HFrEF or HFrEF and recent myocardial infarction.

2. β-BLOCKERS

Bisoprolol, carvedilol, metoprolol

- 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.

- Carvedilol is a nonselective β-adrenoreceptor antagonist that also blocks α-adrenoreceptors, whereas bisoprolol and metoprolol succinate are β1-selective antagonists.

- β-Blockade is recommended for all patients with chronic, stable HF.

- Bisoprolol, carvedilol, and metoprolol succinate reduce morbidity and mortality associated with HFrEF.

- Treatment should be started at low doses and gradually titrated to target doses based on patient tolerance and vital signs.

3. Diuretics

Bumetanide, furosemide, torsemide, metolazone

- 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.
- As diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess.

4. Vaso- and venodilators

Hydralazine ,isosorbide dinitrate, FDC hydralazine/isosorbide dinitrate

- Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance.

- 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).

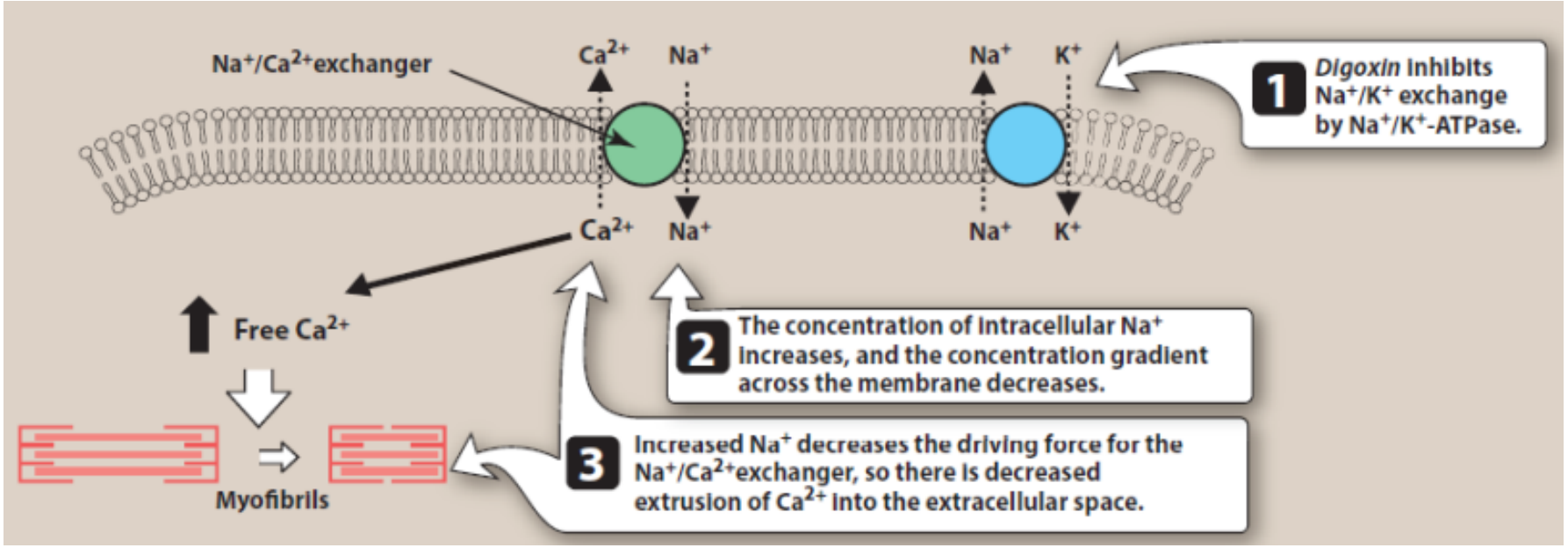
5. Inotropic drugs

A- Digitalis glycosides

- They are a group of chemically similar compounds that can 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 which is seldom used due to its considerable duration of action.



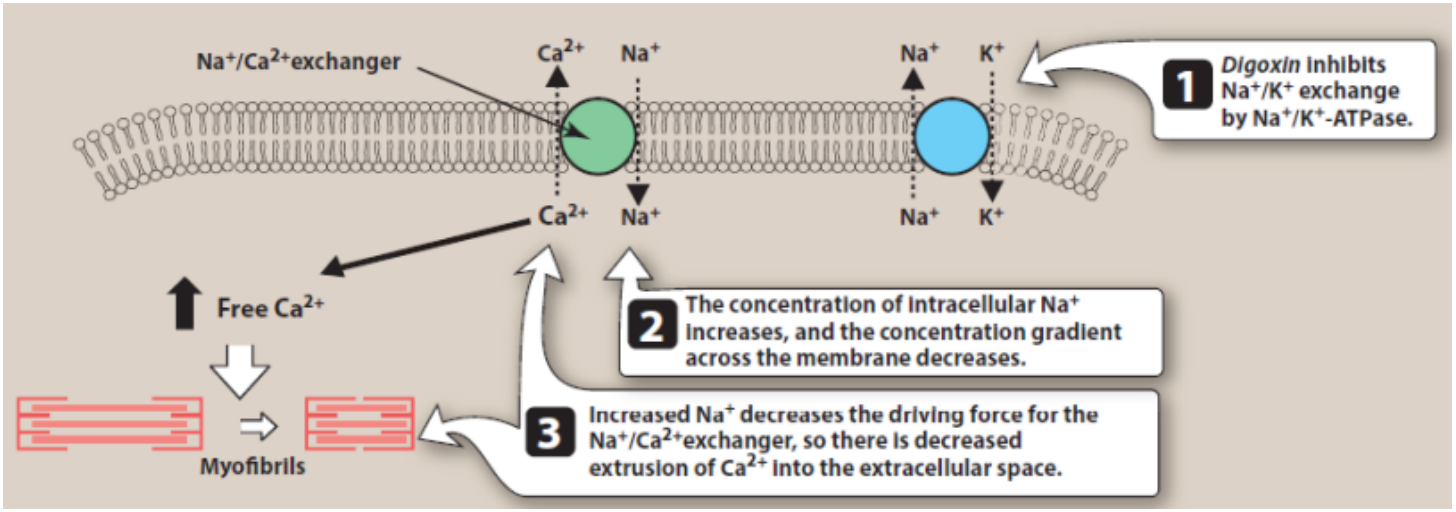
5. Inotropic drugs

Digitalis glycosides

- **Mechanism of action**

A. Regulation of cytosolic calcium concentration: By inhibiting the Na^+/K^+-adenosine triphosphatase (ATPase) enzyme, digoxin reduces the ability of the myocyte to actively pump Na^+ from the cell. This decreases the Na^+ concentration gradient and, consequently, the ability of the Na^+/Ca^{2+}-exchanger to move calcium out of the cell.

- Further, the higher cellular Na+ is exchanged for extracellular Ca^{2+} by the Na^+/Ca^{2+}-exchanger, increasing intracellular Ca^{2+}. A small but physiologically important increase occurs in free Ca^{2+} that is available at the next contraction cycle of the cardiac muscle, thereby increasing cardiac contractility.
- When Na^+/K^+-ATPase is markedly inhibited by digoxin, the resting membrane potential may increase, which makes the membrane more excitable, increasing the risk of arrhythmias (toxicity).



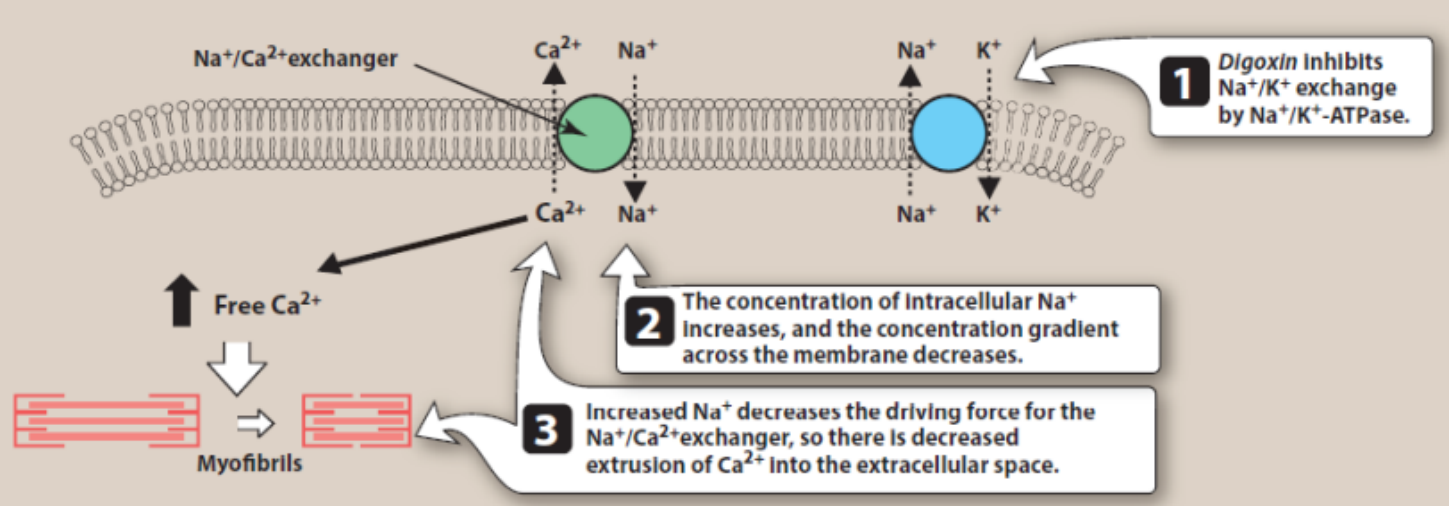
5. Inotropic drugs

Digitalis glycosides

- **Mechanism of action**

B. Increased contractility of the cardiac muscle: 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.

C. Neurohormonal inhibition: Although the exact mechanism of this effect has not been elucidated, 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.



5. Inotropic drugs

Digitalis glycosides

Therapeutic uses:

- Digoxin therapy is indicated in patients with severe HFrEF after initiation of ACE inhibitor, β-blocker, and diuretic therapy.

- Digoxin is not indicated in patients with diastolic or rightsided 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.

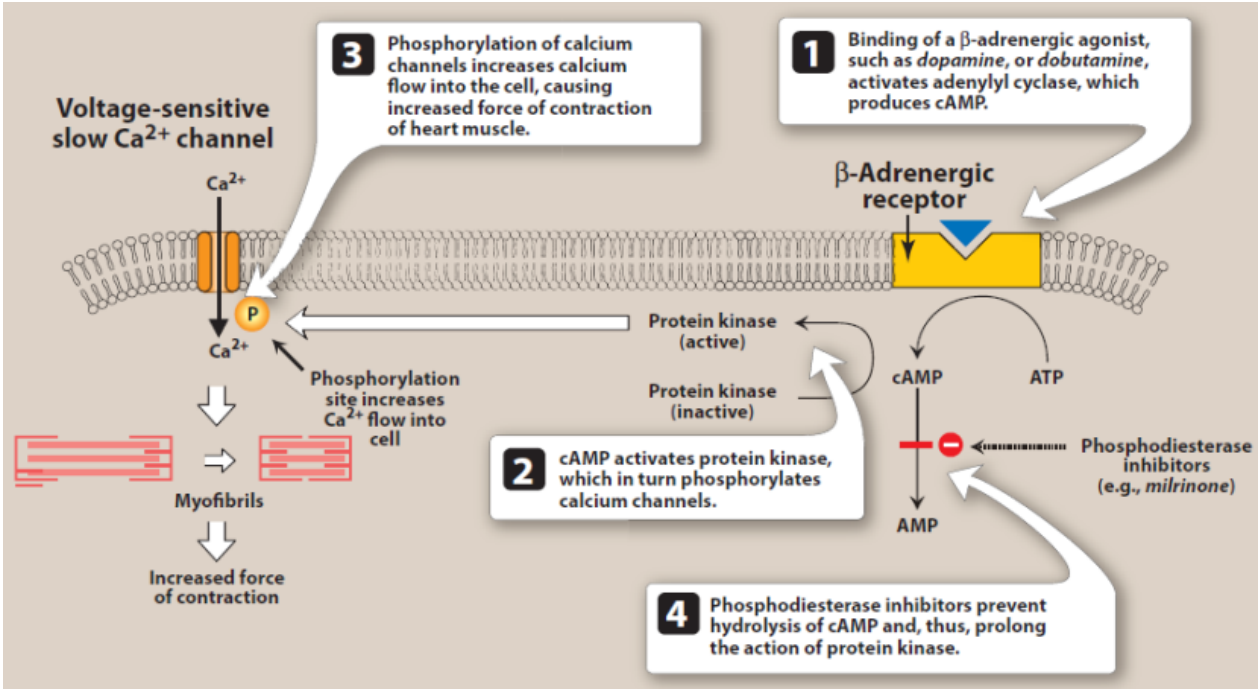
5. Inotropic drugs

B- β-Adrenergic agonists (dobutamine and dopamine)

- β-Adrenergic agonists improve cardiac performance by causing positive inotropic effects and vasodilation.

- 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.

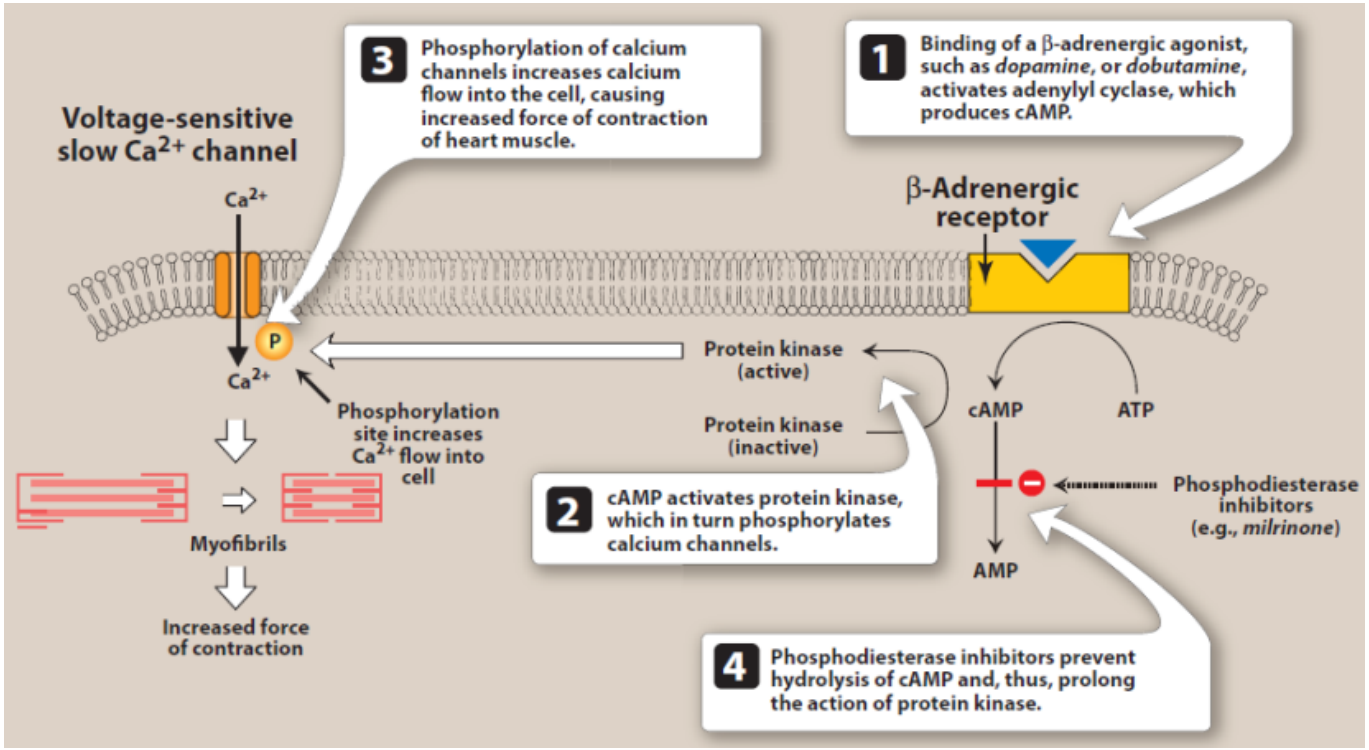
- Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute HF in the hospital setting.



5. Inotropic drugs

B- Phosphodiesterase inhibitors (Milrinone)

- Milrinone is 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. However, 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.



Order of therapy

- In patients with overt HF, loop diuretics are often introduced first for relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema.

- ACE inhibitors or ARBs (if ACE inhibitors are not tolerated) are added after the optimization of diuretic therapy.

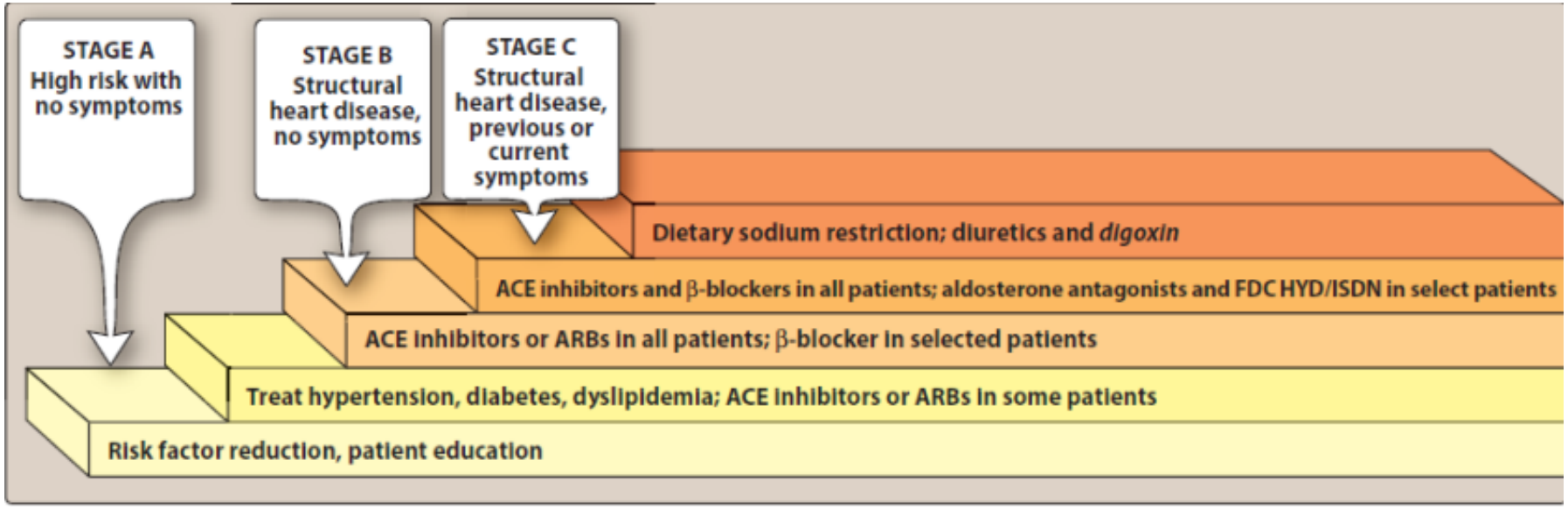
- The dosage is gradually titrated to that which is maximally tolerated and/or produces optimal cardiac output.

- Most patients newly diagnosed with HFrEF are initiated on both low doses of an ACE inhibitor and β-blocker after initial stabilization.

- These agents are slowly titrated to optimal levels to increase tolerability.

- Digoxin, aldosterone antagonists, and fixed-dose hydralazine and isosorbide dinitrate are initiated in patients who continue to have HF symptoms despite optimal doses of an ACE inhibitor and β-blocker.

Order of therapy

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