Drugs used in treatment of Cardiovascular System

Heart Failure

Dr Qutaiba Ghanim Karwi
Department of Pharmacology
College of Medicine
University of Diyala

- 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 due to an impaired ability of the heart to adequately fill with and/or eject blood.

- Main symptoms are dyspnea, fatigue, and fluid retention.

- Left systolic dysfunction secondary to coronary artery disease is the most common cause of HF, accounting for nearly 70 percent of all cases.

- The number of newly diagnosed patients with HF is increasing, because more individuals now survive acute myocardial infarction.

Compensatory mechanism in HF

1. **Neuro-hormonal reflex:** involves:

a- The sympathetic nerous system.

b- The renin-angiotensin-aldosterone system.

- These compensatory mechanism increase the work of the heart and can further contribute to the decline in the cardiac function.

2. **Myocardial hypertrophy:**

Is the most important intrinsic compensatory mechanism where the myocardial mass helps to maintain cardiac performance in the phase of pressure or volume overload. However, after initial beneficial effect, hypertrophy can lead to *ischemic changes, impairment of diastolic filling and alteration in ventricular geometry (remodeling)* due to proliferation of abnormal myocardial cells which die at the accelerated rate leaving the remaining myocardial cells subject to even greater overload.

Goals of treatment

1. Decrease preload and afterload on the myocardium.
2. Decrease extracellular fluid volume.
3. Increase cardiac contractility.
4. Decrease the remodelling of cardiac tissue.

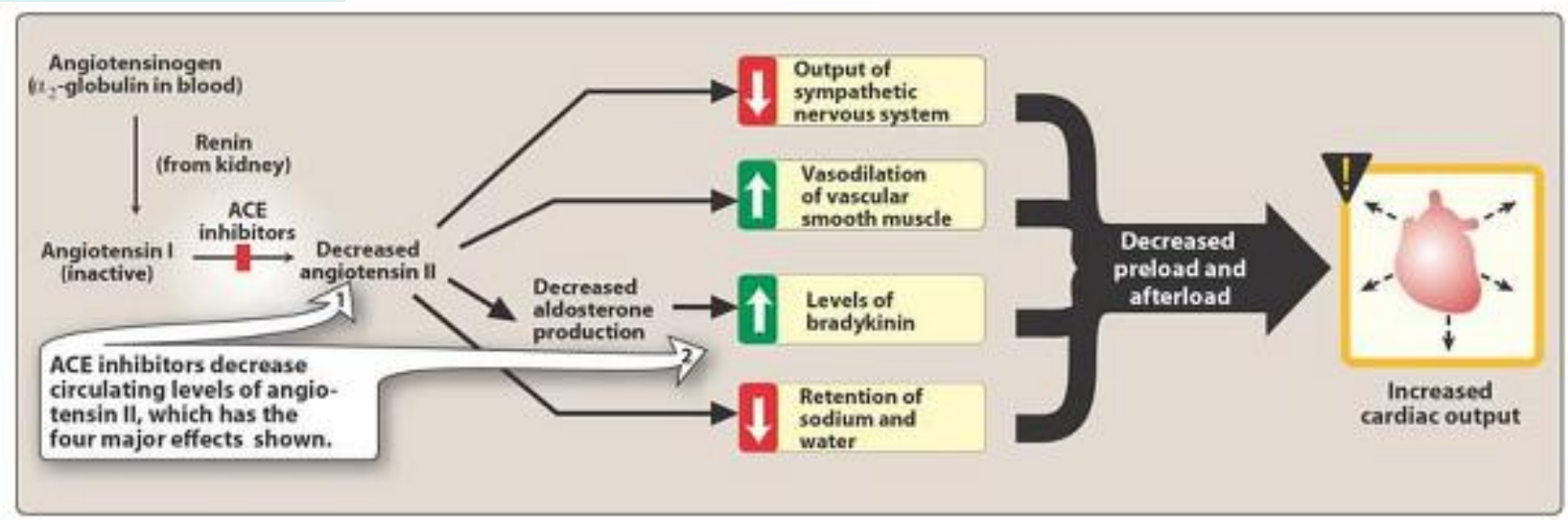
Inhibition of the Renin-Angiotensin (R-A) System

- HF leads to activation of the renin-angiotensin system via two mechanisms:

1) Increased renin release by juxtaglomerular cells in renal afferent arterioles

2) renin release by the juxtaglomerular cells is promoted by sympathetic stimulation (β-receptor).

- High levels of Ang II and of Aldo favours remodelling, fibrosis, and inflammatory changes.



Angiotensin-converting enzyme (ACE) inhibitors

Captopril, Enapril, Fosinopril, Lisinopril, Quinapril and Ramipril

- ACE inhibitors are the agents of choice in HF.
- These drugs block the production of angiotensin II (Aldo as a result) and diminish the rate of bradykinin inactivation.
- Actions on the heart: ACE inhibitors decrease vascular resistance, venous tone, and blood pressure, resulting in an increased cardiac output.
- The use of ACE inhibitors in the treatment of HF has significantly decreased both morbidity and mortality.

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Indications:

1. ACE inhibitors may be considered for single-agent therapy in patients who present with mild dyspnea on exertion and do not show signs or symptoms of volume overload.

2. ACE inhibitors are useful in decreasing HF in asymptomatic patients with an ejection fraction of less than 35 % (left ventricular dysfunction, normal value 50-75%).

3. Early use of ACE inhibitors is indicated in patients with all stages of left ventricular failure, with and without symptoms, and therapy should be initiated immediately after myocardial infarction.

ACE inhibitors: Pharmacokinetics

- The presence of food may decrease absorption, so they should be taken on an empty stomach.
- Except for captopril, ACE inhibitors are prodrugs that require activation by hydrolysis via hepatic enzymes.
- Renal elimination of the active moiety is important for most ACE inhibitors, an exception being Fosinopril.
- Plasma half-lives of active compounds vary from 2 to 12 hours, although the inhibition of ACE may be much longer.
- The newer compounds such as Ramipril and Fosinopril require only once-a-day dosing.

Angiotensin-receptor blockers (ARBs)

Candesartan, Losartan, Telmisartan and Valsartan

- ARBs are extremely potent competitive antagonists of the angiotensin type 1 receptor.
- Although ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical.
- Their use in HF is as a substitute for ACE inhibitors in those patients with severe cough or angioedema.
- **Pharmacokinetics:** All the drugs are orally active and require only once-a-day dosing. Losartan differs from the others in that it undergoes extensive first-pass hepatic metabolism, including conversion to its active metabolite. The other drugs have inactive metabolites.
- All are highly plasma protein bound (> 90%) and, except for candesartan, have large volumes of distribution.

β-Blockers

Atenolol, Carvedilol, Metoprolol

- Decrease the heart rate, inhibit the release of renin, norepinephrine-induced remodelling, hypertrophy and cell death.
- Carvedilol is a nonselective β-adrenoreceptor antagonist that also blocks α-adrenoreceptors
- Metoprolol is a β_1-selective antagonist.
- Carvedilol and metoprolol reduce morbidity and mortality associated with HF.
- Treatment should be titrated.

Diuretics

Bumetanide, Furosemide, Hydrochlorothiazide and 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 the preload and afterload.
- Thiazide diuretics are relatively mild diuretics.
- Loop diuretics are used for patients who require extensive diuresis and those with renal insufficiency.

Direct vasodilators

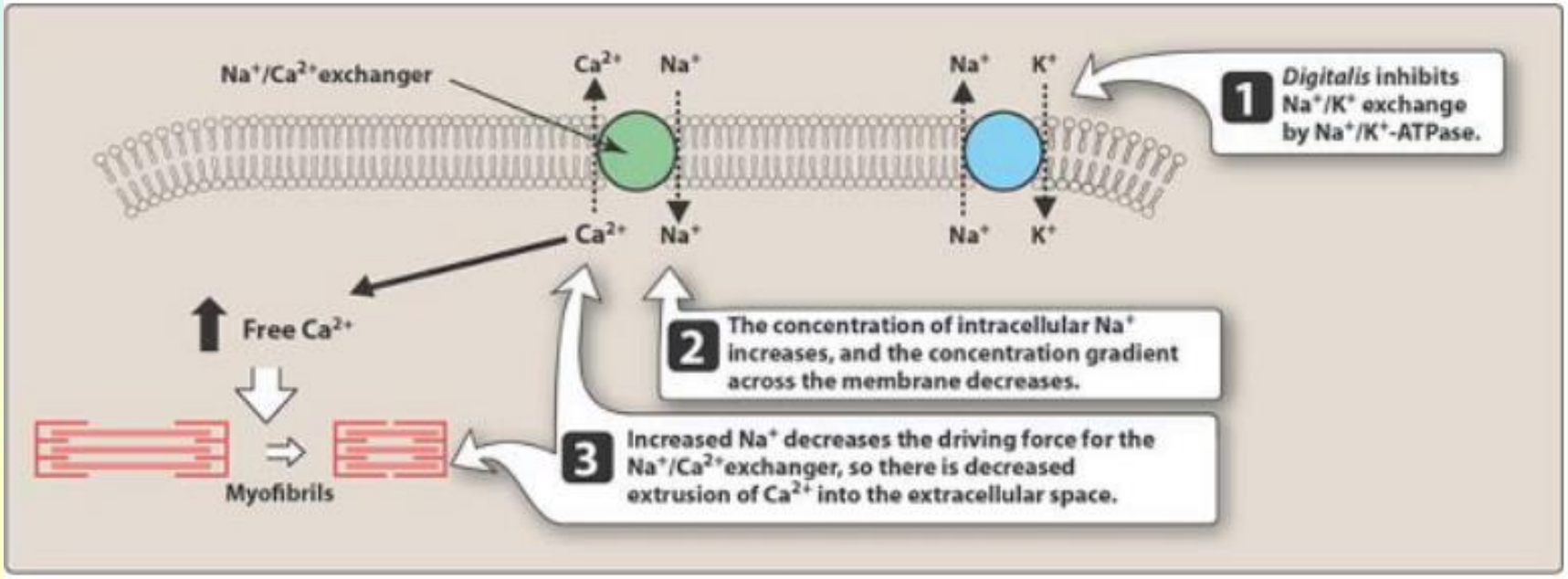
Hydralazine, isosorbide dinitrate and sodium nitroprusside

- Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing the venous capacitance.
- Nitrates are commonly employed venous dilators for patients with congestive HF.
- If the patient is intolerant of ACE inhibitors or β-blockers, the combination of hydralazine and isosorbide dinitrate is most commonly used.

Inotropic drugs

1- Digitalis glycosides

- By inhibiting the ability of the myocyte to actively pump Na^+ from the cell, cardiac glycosides decrease 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 by extracellular Ca^{2+} by the Na^+/Ca^{2+}-exchanger increasing intracellular Ca^{2+}.



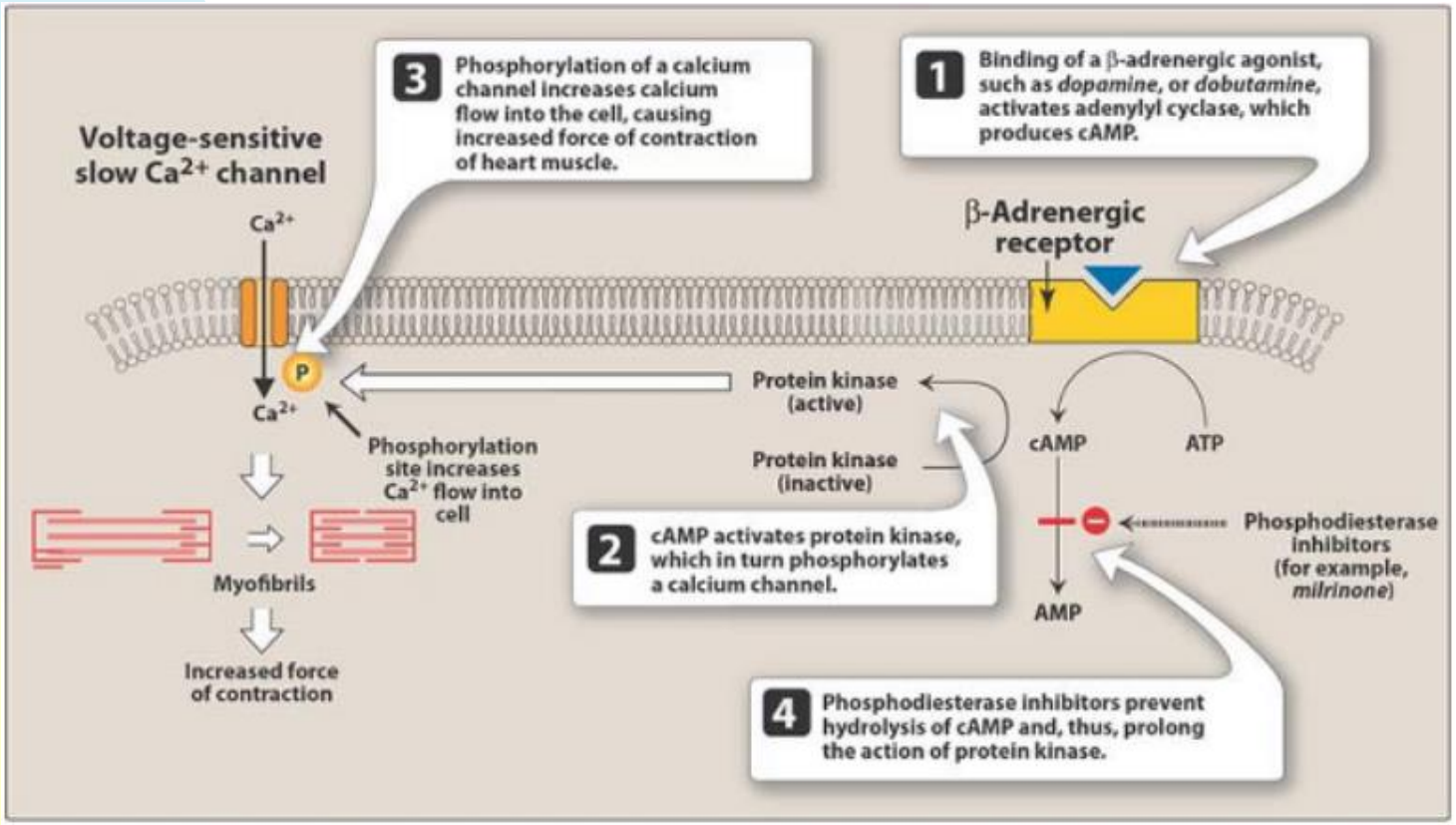
Digoxin: Therapeutic uses

- Digoxin therapy is indicated in patients with severe left ventricular systolic dysfunction after initiation of ACE inhibitor and diuretic therapy.
- Digoxin's major indication is HF with atrial fibrillation.
- Dobutamine, another inotropic agent, can be given intravenously in the hospital, but at present, no effective oral inotropic agents exist other than digoxin.

β-adrenergic agonists

- Dobutamine increases intracellular cyclic adenosine monophosphate (cAMP), activates protein kinase and activates slow Ca^{2+} channels.

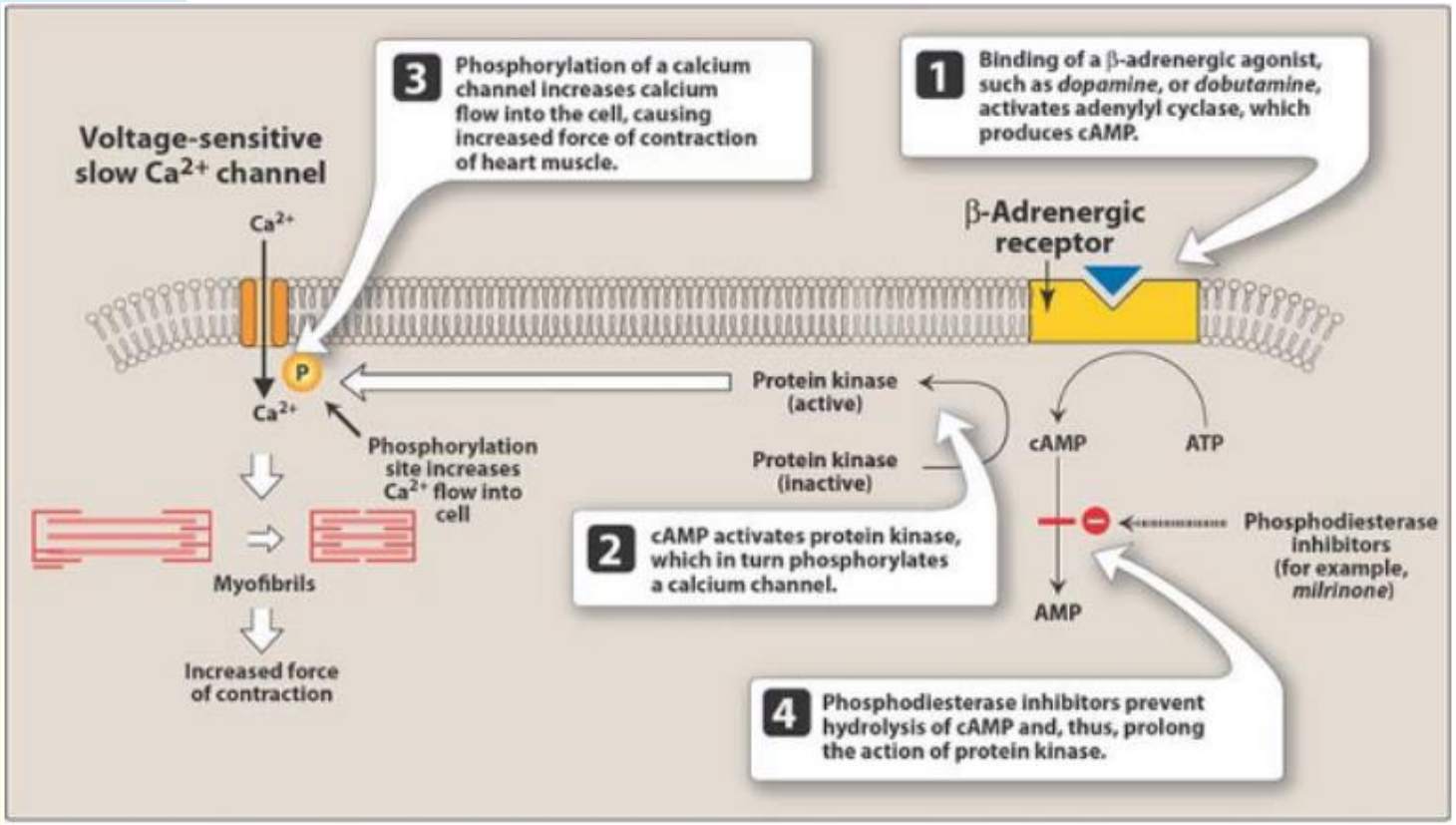
- Given as intravenous infusion to treat acute HF in hospital setting.



Phosphodiesterase inhibitors

Amrinone and Milrinone

- They also increase the intracellular concentration of cAMP. This results in an increase of intracellular calcium and, therefore, cardiac contractility.

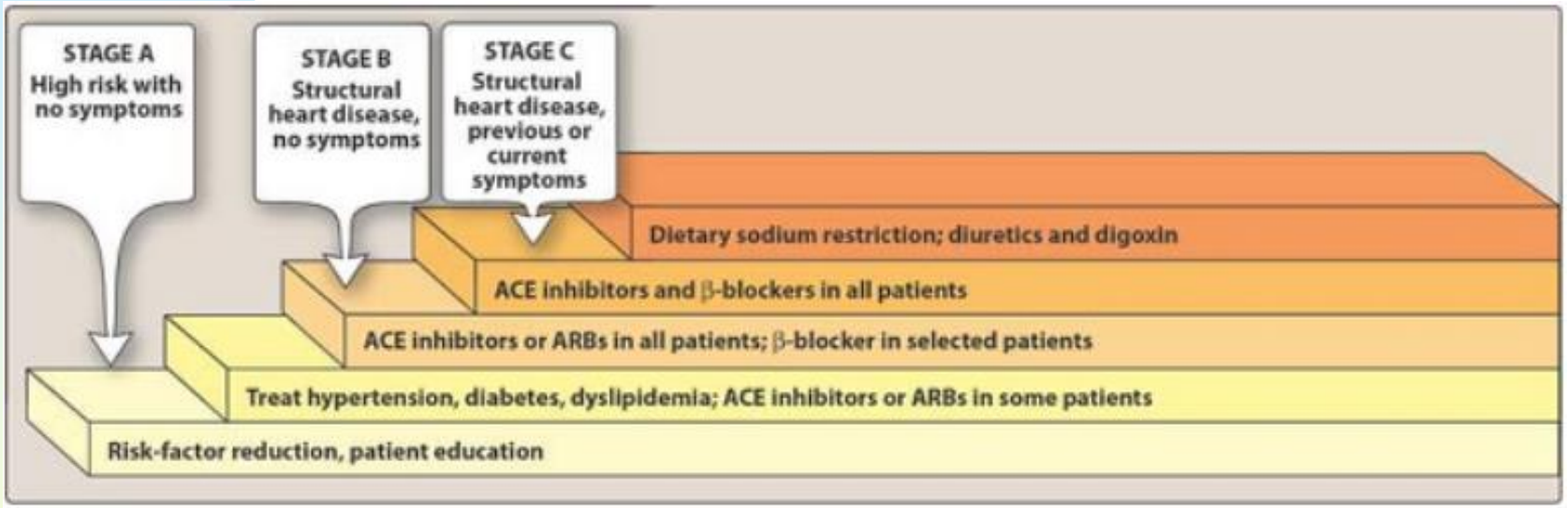


Aldosterone antagonists

Spironolactone and Eplerenone

- Spironolactone is a direct antagonist of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia.
- Because spironolactone promotes potassium retention, patients should not be taking potassium supplements.
- Eplerenone is a competitive antagonist of aldosterone at mineralocorticoid receptors

Order of therapy



End of CHF