Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 5

DRUGS FOR HEART FAILURE

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Overview

- 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**.

Goals of pharmacologic intervention in HF

- **Goals** of treatment are to **alleviate** symptoms, **slow** disease progression, and **improve** survival.
- Pharmacologic intervention provides the following **benefits** in HF:

✓**reduced** myocardial workload

✓**decreased** extracellular fluid volume

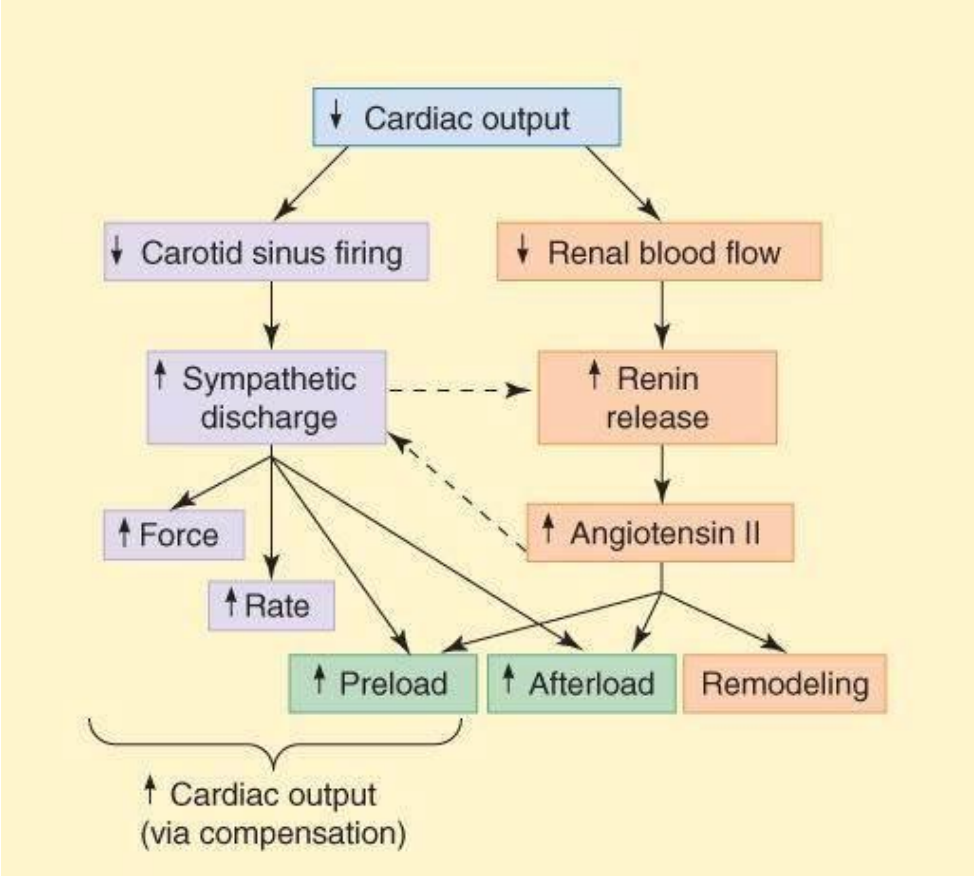
✓**improved** cardiac contractility

✓**reduced** rate of cardiac remodeling

Compensatory physiological responses In HF

1. Increased sympathetic activity:

- **Baroreceptors** sense a **decrease** in BP and **activate** the sympathetic NS.
- The stimulation of **beta-adrenergic receptors** results in an **increased heart rate** and a greater **force** of **contraction** of the heart muscle.
- In addition, **vasoconstriction** enhances **venous return** and increases cardiac **preload**.
- An increase in preload (stretch on the heart) increases **stroke volume**, which, in turn, increases **cardiac output**.
- These compensatory responses **increase the workload** of the heart, which, in the long term, contributes to further **decline** in cardiac function.



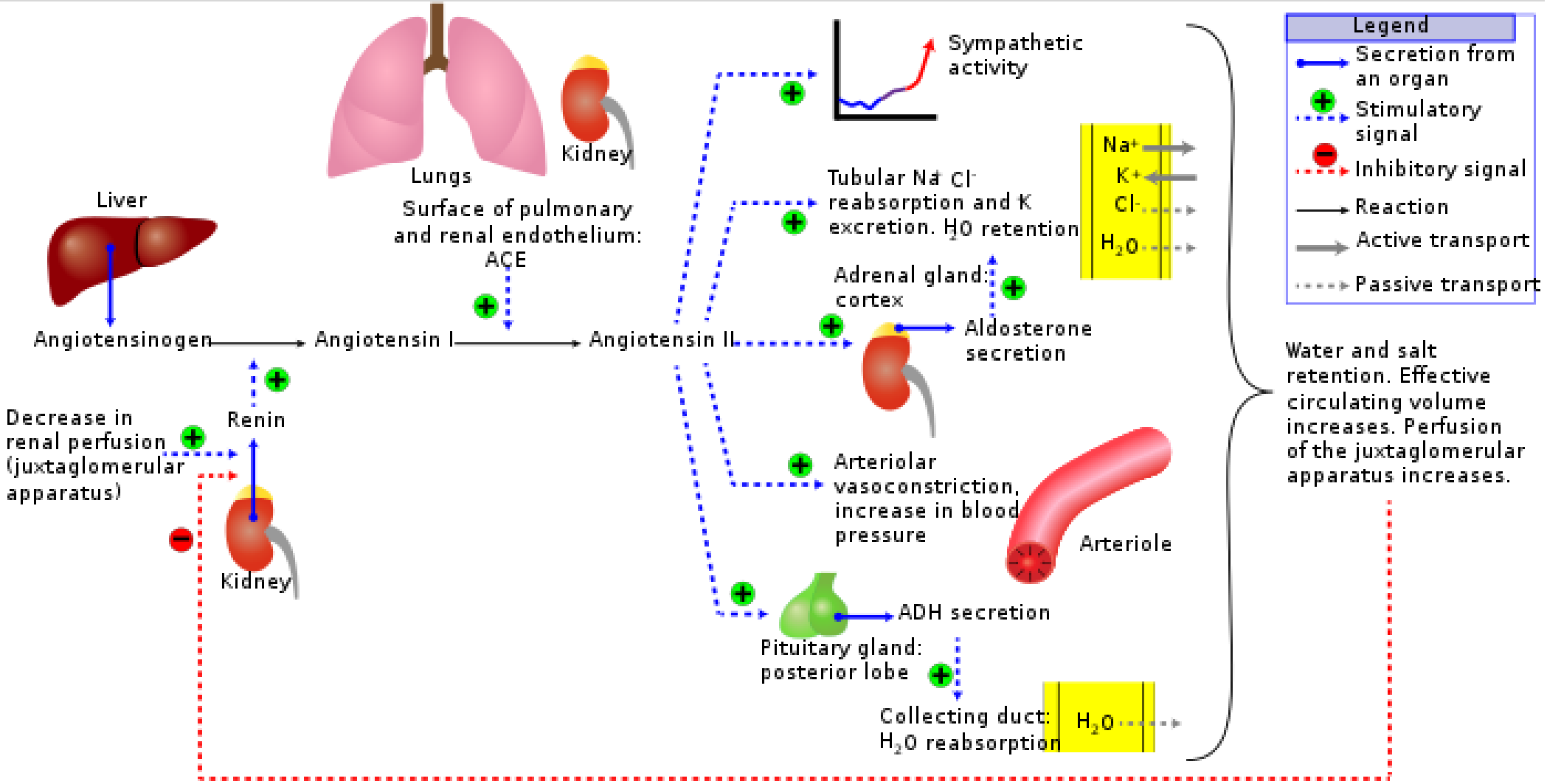
Compensatory physiological responses In HF

2. Activation of the renin-angiotensin-Aldosterone syste (RAAS):

- A **fall** in cardiac output **decreases** blood flow to the kidney, prompting the **release of renin**.
- Renin release is **also** stimulated by **increased sympathetic** activity resulting in increase formation of **angiotensin II** and **release of aldosterone**.
- This result in **increased peripheral resistance** (afterload) and **retention** of sodium and water.
- **Blood volume increases**, and more blood returned to the heart.
- If the heart is **unable** to pump this **extra volume**, venous pressure increases and **peripheral** and **pulmonary edema** occur.
- In addition, high levels of **angiotensin II** and aldosterone have direct detrimental effects on cardiac muscle, favoring **remodeling, fibrosis, and inflammatory** changes.
- Again, these compensatory responses **increase** the workload of the heart, contributing to **further decline** in cardiac function.

Compensatory physiological responses In HF

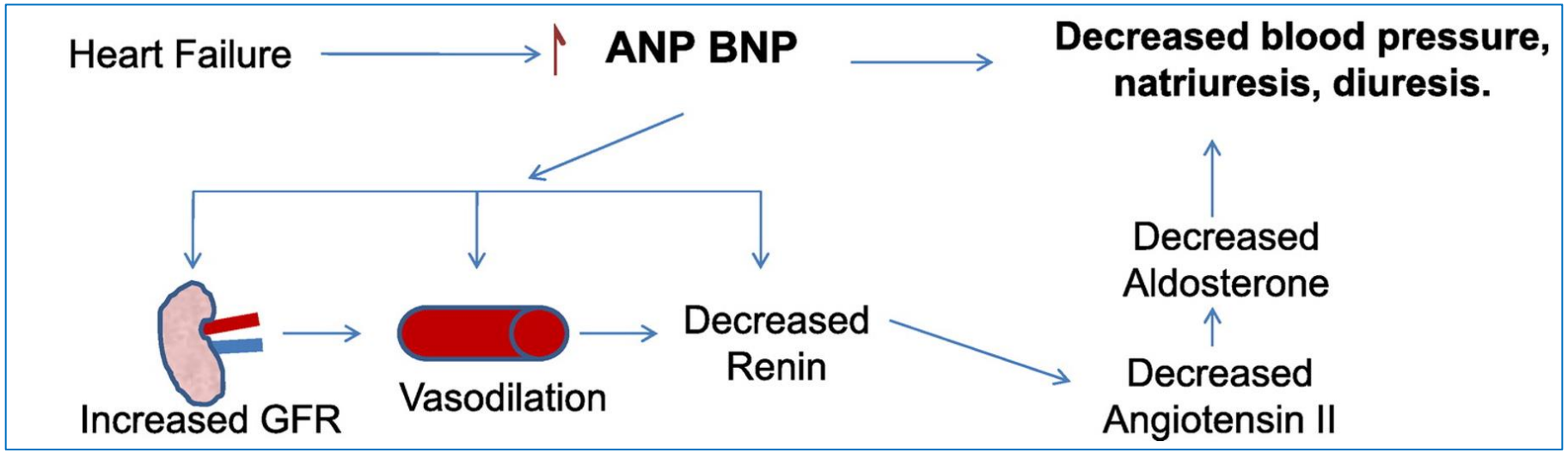
Renin-angiotensin-aldosterone system



Compensatory physiological responses In HF

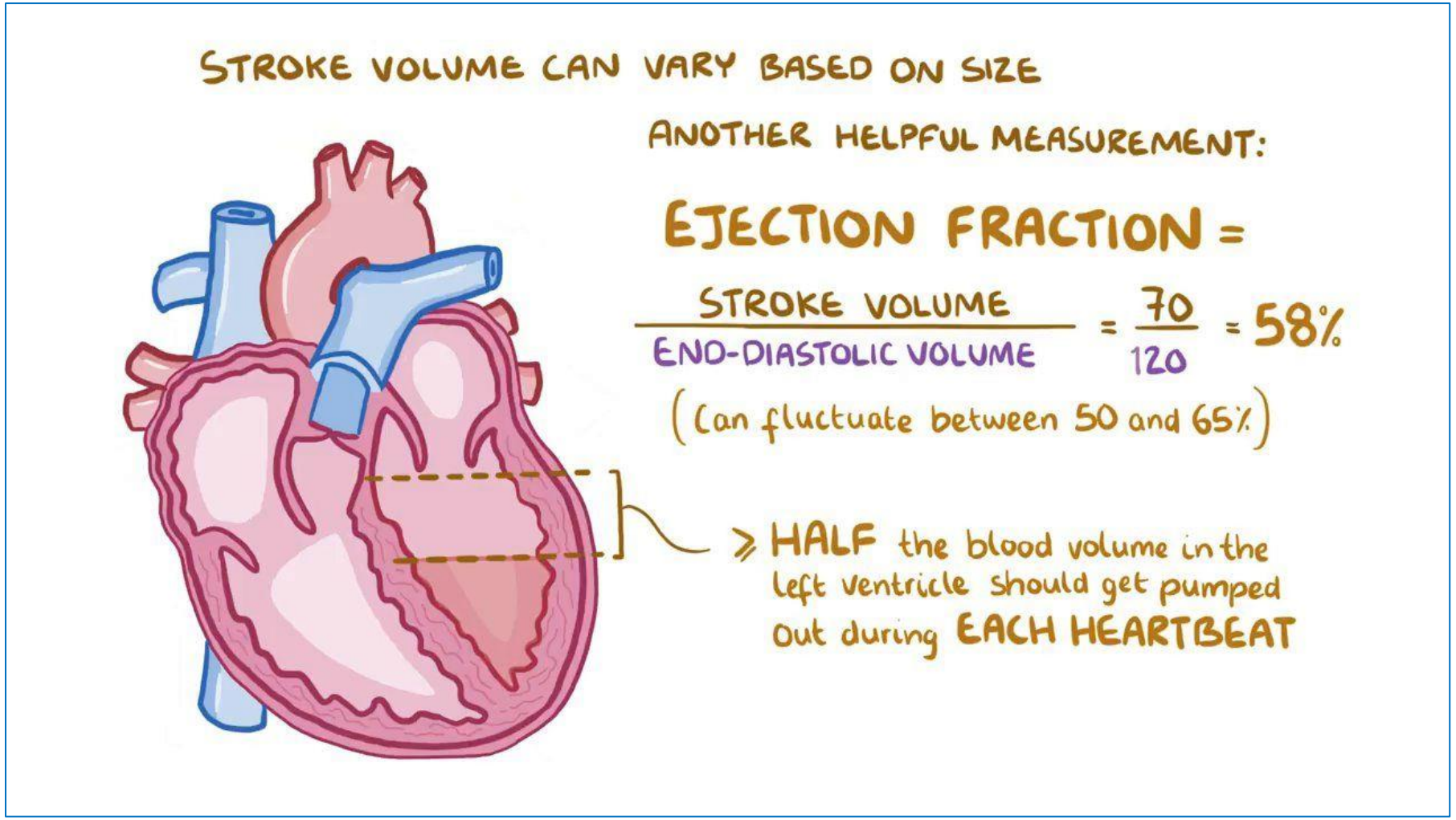
3. Activation of natriuretic peptides:

- An **increase in preload** also increases the **release of natriuretic peptides**.
- Natriuretic peptides, which include **atrial, B-type, and C-type**, have differing roles in HF.
- **Activation** of the natriuretic peptides ultimately results in **vasodilation, natriuresis, inhibition of renin and aldosterone release, and a reduction in myocardial fibrosis**.
- This beneficial response may **improve cardiac function and HF symptoms**.



Compensatory physiological responses In HF

4. Myocardial hypertrophy:



Compensatory physiological responses In HF

4. Myocardial hypertrophy:

- **Initially**, **stretching** of the heart muscle leads to a **stronger** contraction of the heart.
- However, **excessive** elongation of the fibers results in **weaker contractions** and a diminished ability to eject blood.
- This type of failure is termed "**systolic failure**" or HF with reduced ejection fraction (**HFrEF)** and is the result of the **ventricle being unable to pump effectively**.
- Patients with HF may have "**diastolic dysfunction**; a term applied when the **ability of the ventricles to relax and accept blood is impaired** by structural changes such as hypertrophy.
- In this case, the ventricle does not fill adequately, and the inadequacy of cardiac output is termed "**diastolic HF**' or HF with preserved ejection fraction (**HFpEF**).

Acute (decompensated) HF

- If the compensatory mechanisms adequately **restore cardiac output**, HF is said to be **compensated**.
- If the compensatory mechanisms **fail to maintain cardiac output**, HF is **decompensated,** and the patient develops **worsening HF signs and symptoms**.
- **Typical HF signs and symptoms** include **dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and peripheral edema**.

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

✓judicious use of diuretics

Therapeutic strategies In HF

- **Specifically for HFrEF**, inhibitors of the **RAAS**, inhibitors of the **sympathetic** nervous system, and drugs that enhance activity of **natriuretic peptides** have been shown to **improve survival and reduce symptoms**.
- **Inotropic** agents are reserved for **acute** signs and symptoms of HF and are used mostly in the **inpatient setting**.
- **Drugs** that may **precipitate** or **exacerbate HF**, such as NSAIDs, alcohol, non-dihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be **avoided** if possible.

Pharmacologic intervention in HF

ACE INHIBITORS

Captopril GENERIC ONLY
Enalapril VASOTEC
Fosinopril GENERIC ONLY
Lisinopril PRINIVIL, ZESTRIL
Quinapril ACCUPRIL
Ramipril ALTACE

ANGIOTENSIN RECEPTOR BLOCKERS

Candesartan ATACAND
Losartan COZAAR
Telmisartan MICARDIS
Valsartan DIOVAN

ARNI

Sacubitril/valsartan ENTRESTO

ALDOSTERONE ANTAGONISTS

Eplerenone INSPRA
Spironolactone ALDACTONE

β–ADRENORECEPTOR BLOCKERS

Bisoprolol GENERIC ONLY
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 GENERIC ONLY
Isosorbide dinitrate DILATRATE-SR, ISORDIL
FDC Hydralazine/Isosorbide dinitrate BIDIL

HCN CHANNEL BLOCKER

Ivabradine CORLANOR

INOTROPIC AGENTS

Digoxin LANOXIN
Dobutamine DOBUTREX
Dopamine GENERIC ONLY
Milrinone GENERIC ONLY

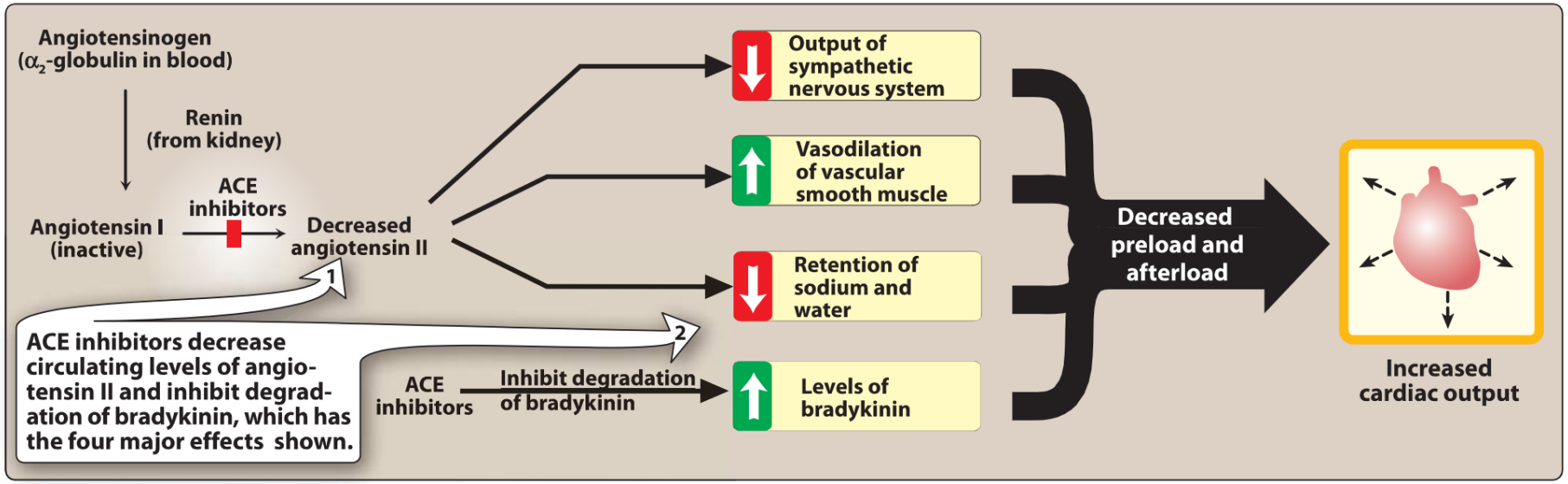
B-TYPE NATRIURETIC PEPTIDE

Nesiritide NATRECOR

1. ACE Inhibitors

MECHANISM OF ACTION:

- ACE inhibitors **decrease** vascular resistance (**afterload**) and venous tone (**preload**), resulting in **increased cardiac output**.
- ACE inhibitors also **diminish** the usual angiotensinII-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. ACE Inhibitors

THERAPEUTIC USES:

- ACE inhibitors may be considered for patients with **asymptomatic and symptomatic HFrEF**.
- ACE inhibitors are **indicated** for patients with **all stages of left ventricular failure**.
- These agents should be **started at low doses** and titrated to target or maximally tolerated doses in the management of HFrEF.
- ACE inhibitors are also used in the treatment of **hypertension.**

1. ACE Inhibitors

PHARMACOKINETICS:

- **Food** may decrease the absorption of **captopril**, so it should be taken on an empty stomach.
- **Except** for **captopril** and injectable **enalaprilat**, ACE inhibitors are **prodrugs** that require activation by **hydrolysis** via hepatic enzymes.
- **Renal** elimination of the active moiety is important for most ACE inhibitors **except fosinopril**, which also undergoes excretion in the **feces**.
- Plasma **half-lives** of active compounds vary from **2 to 12 hours**, although the **inhibition** of **ACE** may be much **longer**.

1. ACE Inhibitors

ADVERSE EFFECTS:

- These include **postural hypotension, renal insufficiency, hyperkalemia, a persistent dry cough, and angioedema** (**rare**).
- Because of the risk of **hyperkalemia**, potassium levels must be monitored, particularly with concurrent use of potassium supplements, potassium-sparing diuretics, or aldosterone antagonists.
- **Serum creatinine** levels should also be monitored, particularly in patients with underlying renal disease.
- The potential for **symptomatic hypotension** with ACE inhibitors is much more common if used concomitantly with a **diuretic**.
- ACE inhibitors are **teratogenic** and should not be used in pregnant women.

2. Angiotensin receptor blockers

- Angiotensin receptor blockers (ARBs) are **orally active compounds** that are **competitive antagonists** of the angiotensin II type 1 receptor.
- However, ARBs do **not affect bradykinin** levels.
- Although ARBs have actions **similar to those of ACE inhibitors**, they are **not** therapeutically **identical**, so, ARBs are a substitute for patients who **cannot tolerate ACE inhibitors**.
- ARBs are orally active and are dosed **once daily**, with the **exception of valsartan**, which is dosed **twice** daily.
- **Losartan** differs in that it undergoes **extensive first-pass** hepatic metabolism, including conversion to an **active metabolite**.
- The **other** drugs have **inactive metabolites**.
- Like ACE inhibitors, ARBs are **contraindicated** in **pregnancy**
-

3. Aldosterone receptor antagonists

- Patients with HF have **elevated levels of aldosterone** due to angiotensin II stimulation and reduced hepatic clearance of the hormone.
- Spironolactone and eplerenone are **antagonists of aldosterone** at the mineralocorticoid receptor, thereby **preventing salt retention, myocardial hypertrophy, and hypokalemia**.
- **Spironolactone** also has affinity for **androgen and progesterone receptors and** is associated with endocrine-related adverse effects such as **gynecomastia** and **dysmenorrhea**.
- Aldosterone antagonists are indicated in patients with **symptomatic HFrEF or HFrEF and recent myocardial infarction**.

4. Beta-Blockers

- The **benefits** of beta-blockers in HF is attributed to their ability to :

1. **prevent** the changes that occur because of chronic activation of the sympathetic nervous system.
2. **decrease** heart rate and inhibit the release of renin in the kidneys.
3. **prevent** the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.

- **Bisoprolol, carvedilol**, and long-acting **metoprolol** succinate reduce morbidity and mortality associated with HFrEF.
- They should be used **with caution** with other drugs that **slow AV conduction**, such as **amiodarone, verapamil, and diltiazem**.

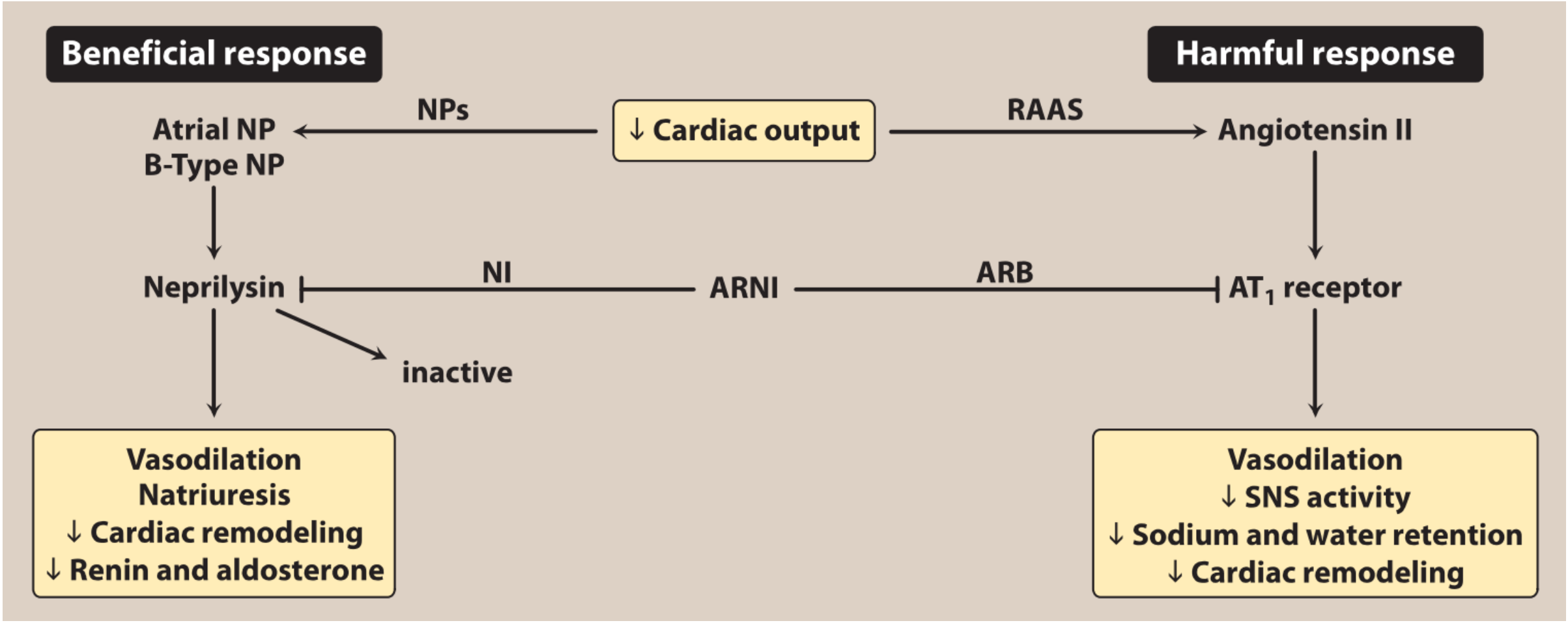
5. DIURETICS

- Diuretics **reduce signs and symptoms** of volume overload, such as dyspnea on exertion, orthopnea, and peripheral edema.
- Diuretics **decrease plasma volume** and, subsequently, **decrease venous return** to the heart (**preload**).
- Diuretics may also **decrease afterload** by reducing plasma volume, thereby decreasing blood pressure.
- **Loop** diuretics are the most **commonly** used diuretics in HF.
- Since diuretics have **not been shown to improve survival** in HF, they should only be used to treat signs and symptoms of volume excess.

6. ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR

- **Sacubitril/valsartan** combines the actions of an ARB with neprilysin inhibition.
- Inhibition of neprilysin results in **increased concentration of vasoactive peptides**, leading to natriuresis, diuresis, vasodilation, and inhibition of fibrosis.
- Together, the combination **decreases afterload, preload, and myocardial fibrosis**.
- An ARNI **improves survival and clinical signs and symptoms** of HF, as compared to therapy with an ACE inhibitor.
- An ARNI should **replace** an ACE inhibitor or ARB in patients with HFrEF who **remain symptomatic on optimal doses** of a B-blocker and an ACE inhibitor or ARB.

6. ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR



7. HCN-GATED CHANNEL BLOCKER

- The hyperpolarization-activated cyclic nucleotide-gated (HCN) channel is responsible for the **I_f current and setting the pace within the SA node**.
- **Inhibition** of the HCN channel results in **slowing of depolarization and a lower heart rate** in a use and dose-dependent manner.
- **Ivabradine** is the only approved drug in the class of HCN channel blockers.
- It act by selectively slowing the I_f current in the SA node, reduction of heart rate occurs without a reduction in contractility, AV conduction, ventricular repolarization, or blood pressure.
- In patients with **HFrEF**, a slower heart rate increases stroke volume and improves symptoms of HF.
- Ivabradine should **not** be used in **pregnancy** or **breast-feeding**.

8. VASO- AND VENODILATORS

- **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 ARBs, 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.
- Headache, dizziness, and hypotension are common **adverse effects** with this combination.
- Rarely, **hydralazine** has been associated with **drug-induced lupus**.

9. INOTROPIC DRUGS

- **Positive inotropic agents** enhance cardiac **contractility** and, thus, increase cardiac **output via** increased cytoplasmic calcium concentration of cardiac muscle.
- **All** positive inotropes in HFrEF that **increase intracellular calcium conc**. have been associated with **reduced survival**, especially in patients with HFrEF.
- For this reason, these agents, with the exception of digoxin, are **only used for a short period** mainly in the inpatient setting.
- They include **Digitalis glycosides** (digoxin), **B-Adrenergic agonists** (dobutamine& dopamine), and **Phosphodiesterase inhibitors** (Milrinone)

9. INOTROPIC DRUGS

POSITIVE INOTROPIC MEDICATIONS

↑ STRENGTH of HEART MUSCLE CONTRACTION

↓

↑ STROKE VOLUME

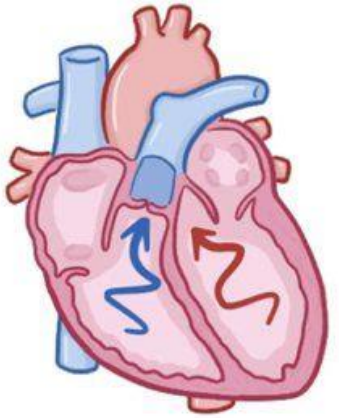
↓

↑ CARDIAC OUTPUT

heart can't pump enough blood to the body's tissues

(e.g. systolic heart failure)

* CARDIAC GLYCOSIDES (e.g. digoxin)
* BETA AGONISTS (e.g. dobutamine)
* PHOSPHODIESTERASE INHBITORS (e.g. milrinone)

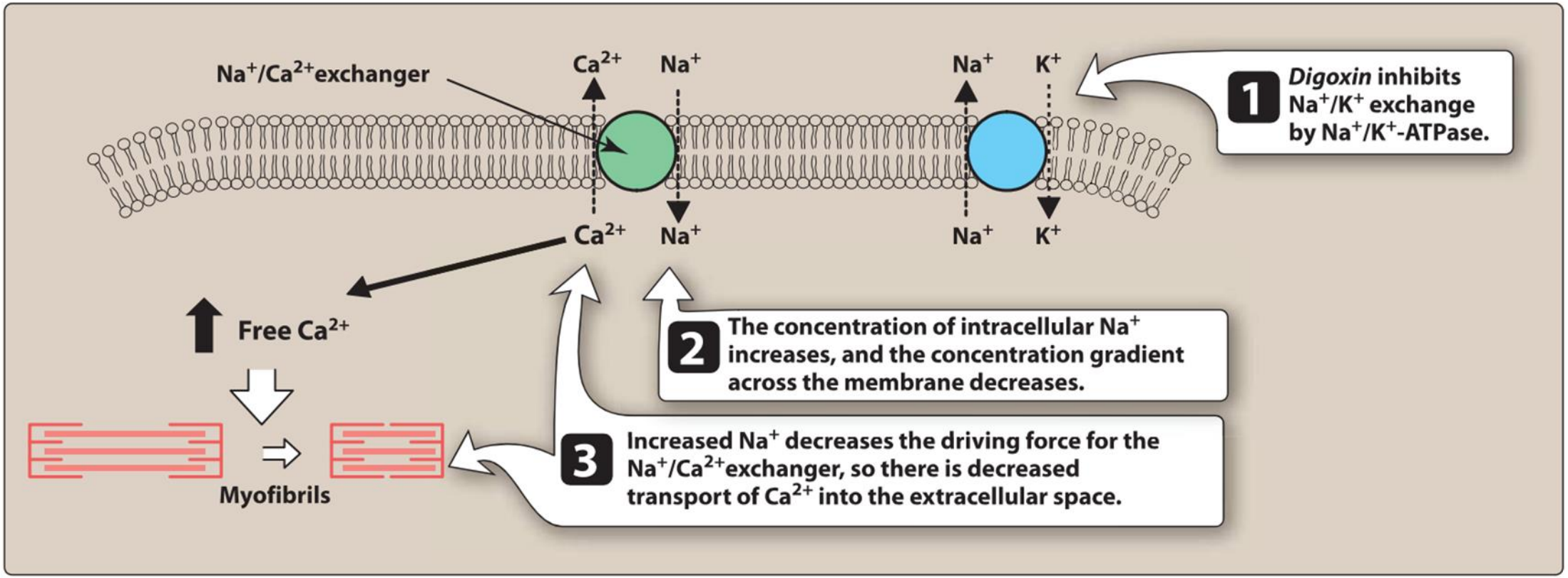


9. INOTROPIC DRUGS

Digitalis glycosides (digoxin)

- 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.
- They act By **inhibiting the Na/K ATPase enzyme**, digoxin **reduces** the ability of the myocyte to **actively pump Na+** from the cell.
- This ultimately results in a small but physiologically important **increase in free $Ca2^{+,}$** thereby leading to **increased cardiac contractility** 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 has a **long half-life of 30 to 40 hours**. It is mainly eliminated intact by the **kidney**, requiring **dose adjustment in renal dysfunction**.

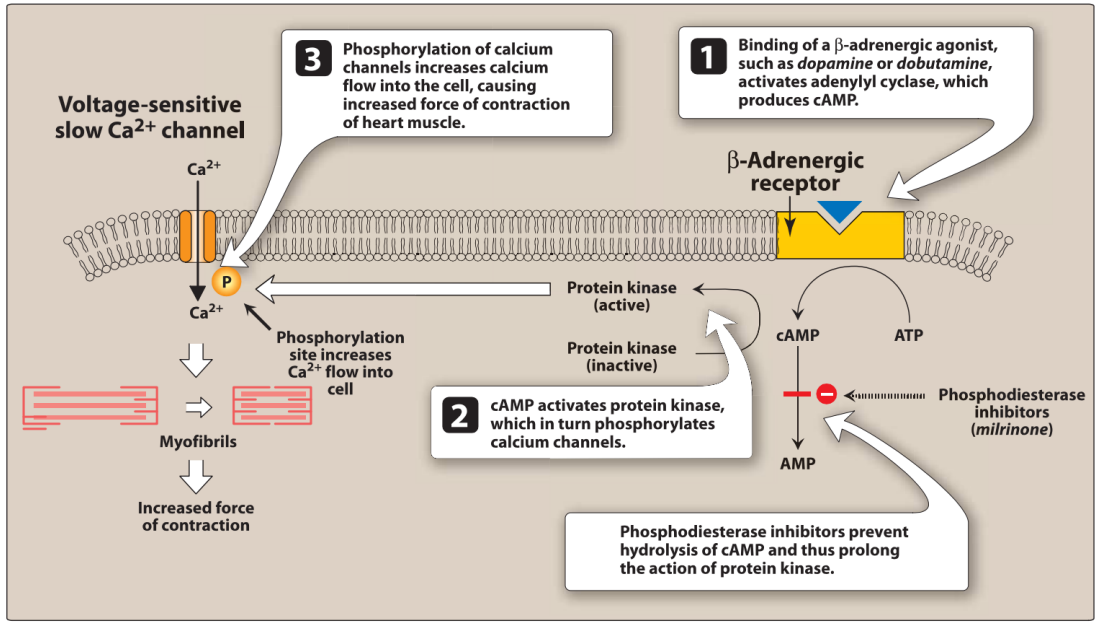
Digitalis glycosides (digoxin)



9. INOTROPIC DRUGS

Beta-Adrenergic agonists:

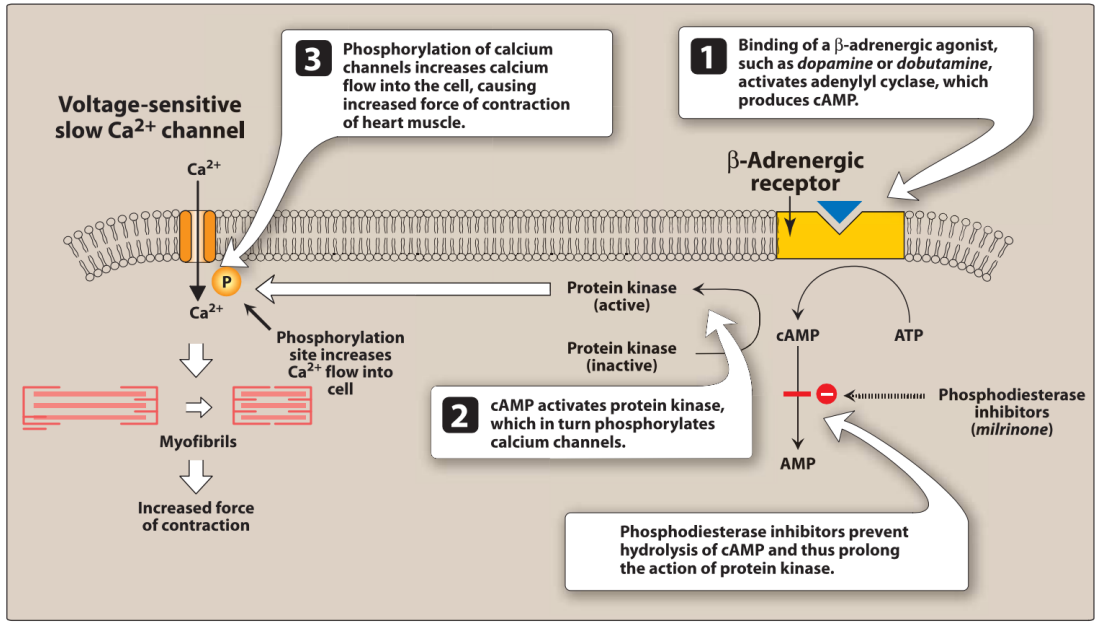
- Beta-adrenergic agonists, such as dobutamine and dopamine **improve** cardiac performance by causing **positive inotropic effects and vasodilation**.
- Beta-adrenergic agonists ultimately lead to **increased entry of calcium ions** into myocardial cells and **enhanced contraction**.
- Both drugs must be given by **intravenous infusion** and are primarily used in the **short-term** treatment of **acute HF in the hospital setting**.



9. INOTROPIC DRUGS

Phosphodiesterase inhibitors:

- **Milrinone** is a PD inhibitor that **increases** the intracellular conc. of **cAMP**.
- This results in an **increase of intracellular calcium** and, therefore, cardiac **contractility**.
- Milrinone is usually given by **IV infusion for short-term treatment of acute HF**.
- However, **dobutamine and milrinone** may also used for **intermediate-term treatment** in the **outpatient** setting for **palliative care.**



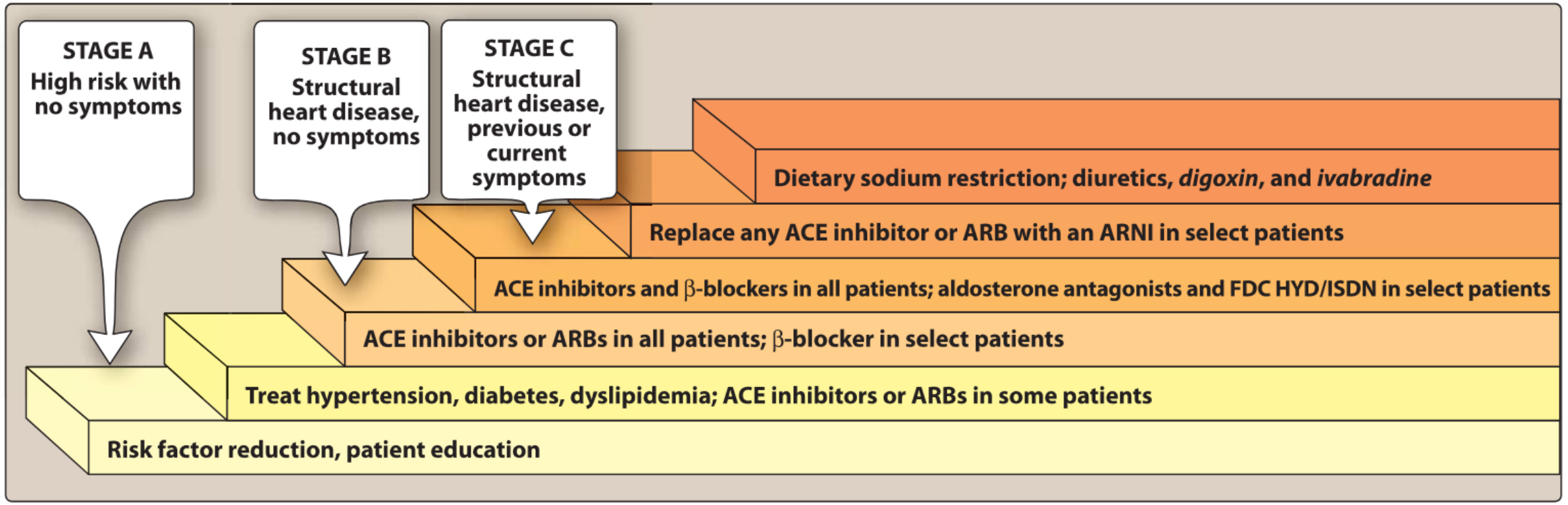
10. RECOMBINANT B-TYPE NATRIURETIC PEPTIDE

- Recombinant B-type natriuretic peptide (BNP), or **nesiritide** can be used in **acute decompensated CHF as an alternative** (when IV diuretics are minimally effective).
- Through **binding** to natriuretic peptide receptors, nesiritide **stimulates** natriuresis and diuresis and **reduces** preload and afterload.
- Nesiritide is administered intravenously as a bolus (most often) and continuous infusion.
- Like endogenous BNP, nesiritide has a short half-life of 20 minutes.
- The most common adverse effects are **hypotension and dizziness**, and like diuretics, nesiritide can **worsen renal function**.

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.
- Historically, **beta-blockers** were added after optimization of ACE inhibitor or ARB therapy;
- However, most patients **newly diagnosed with HFrEF** are initiated on **both** low doses of an ACE inhibitor and beta-blocker after initial stabilization.
- **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 beta-blocker.
- Lastly, **digoxin and ivabradine** are added for **symptomatic benefit only** in patients on optimal HF pharmacotherapy.

ORDER OF THERAPY



Thank You