Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 3

DRUGS FOR HEART FAILURE

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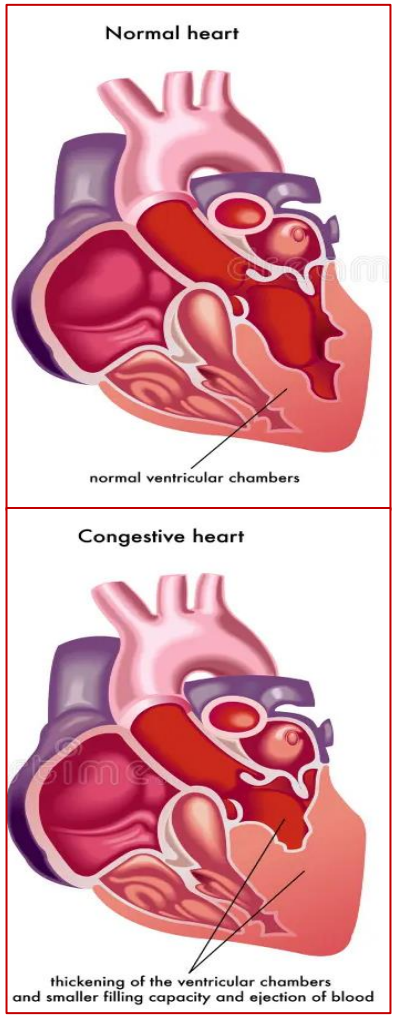
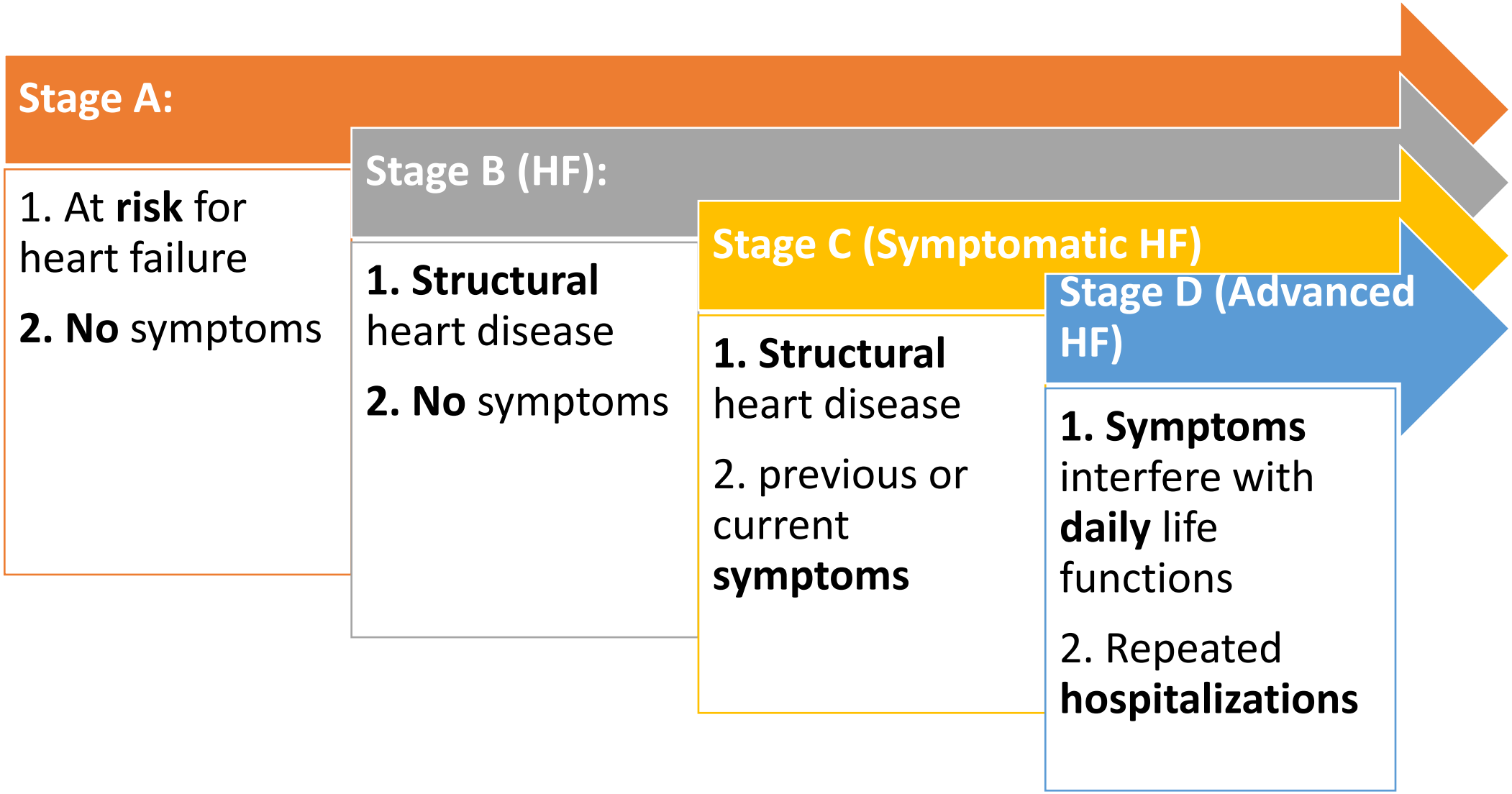
DEFINITION OF HF

- 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**.



CLASSIFICATION OF HF

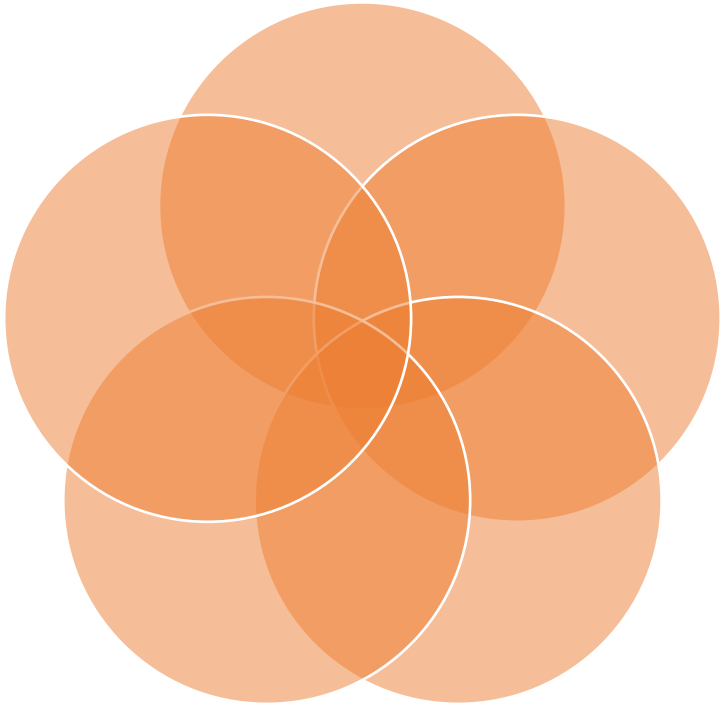


Goals of pharmacologic intervention in HF

Pharmacologic intervention provides the following **benefits** in HF:

4. Reduced rate of cardiac remodeling

1. Reduced myocardial workload



3. Improved cardiac contractility

2. Decreased extracellular fluid volume

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

Compensatory physiological responses In HF

1. Increased sympathetic activity (Baroreceptors)

An **increase** in **preload**, **stroke volume**, **cardiac output**.

These compensatory responses **increase the workload** of the heart, which, in the long term, contributes to further **decline** in cardiac function.

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

This result in **increased afterload** and **retention of sodium and water**.

Again, these compensatory responses **increase** the workload of the heart, contributing to **further decline** in cardiac function.

3. Activation 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**.

4. Myocardial hypertrophy:

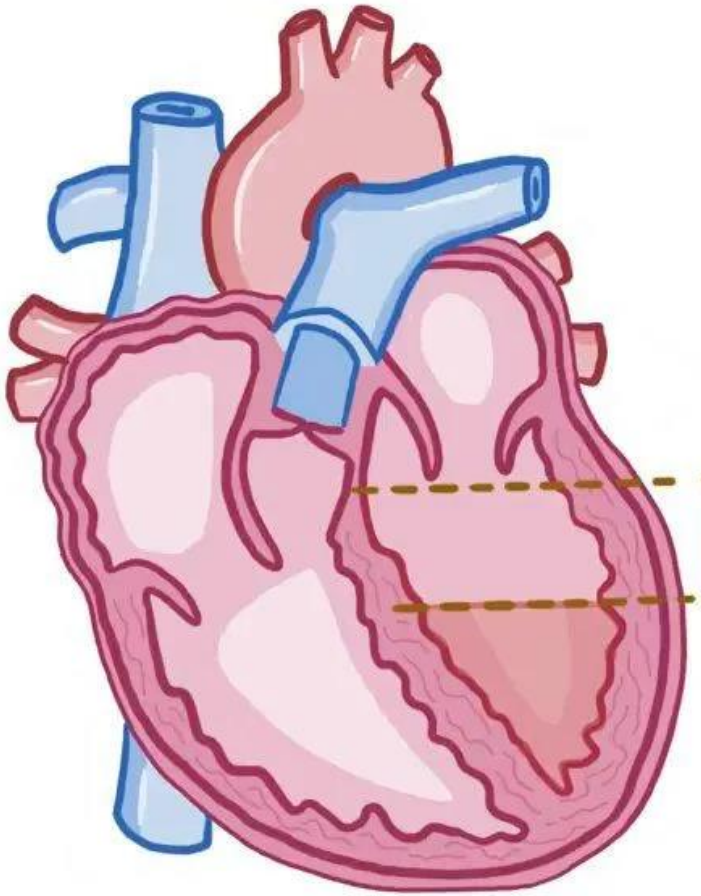
Initially, **stretching** of the heart muscle leads to a **stronger** contraction of the heart.

However, **excessive** elongation of the fibers results in **weaker contractions** and a diminished ability to eject blood.

Ejection Fraction

STROKE VOLUME CAN VARY BASED ON SIZE

ANOTHER HELPFUL MEASUREMENT:



EJECTION FRACTION =

$$\frac{\text{STROKE VOLUME}}{\text{END-DIASTOLIC VOLUME}} = \frac{70}{120} = 58\%$$

(Can fluctuate between 50 and 65%)

≥ **HALF** the blood volume in the left ventricle should get pumped out during **EACH HEARTBEAT**

HFrEF & HFpEF

HFrEF

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**.

HFpEF

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**).

Compensated vs Decompensated (Acute) HF

Compensated HF

- If the compensatory mechanisms adequately **restore cardiac output**, HF is said to be **compensated**.

Decompensated HF

- If the compensatory mechanisms **fail to maintain cardiac output**, HF is **decompensated,** and the patient develops **worsening HF signs and symptoms**.

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)
- **Rx** 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**.

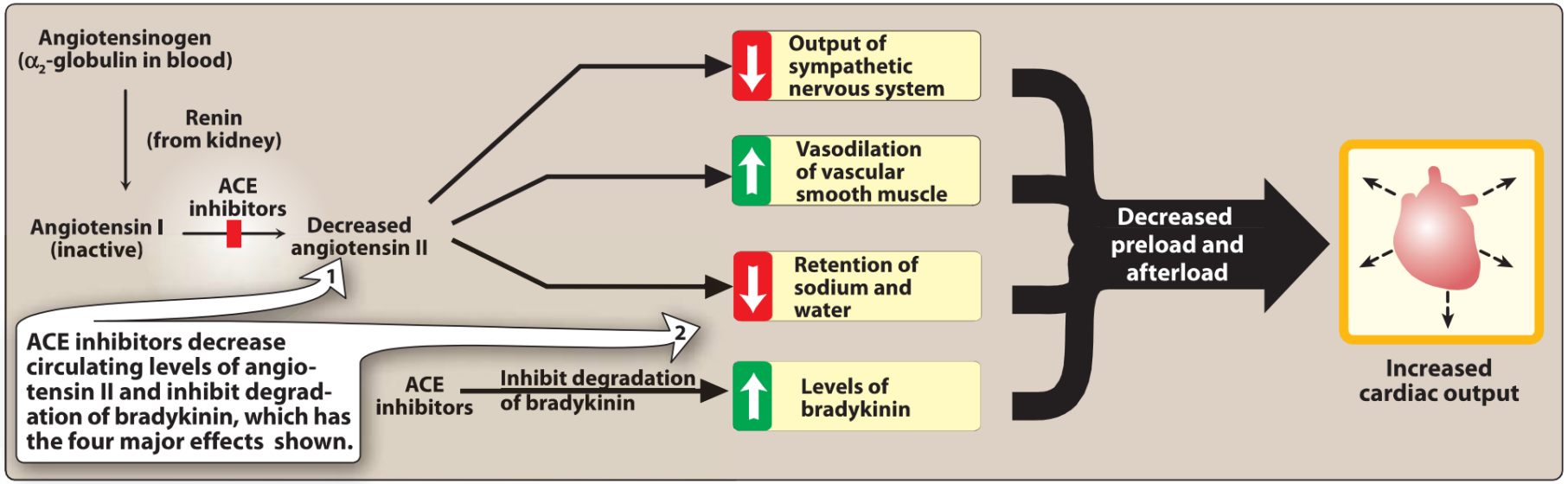
Inotropic agents are reserved for **acute** signs and symptoms of HF and are used mostly in the **inpatient setting**.

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.

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, lisinopril,** and **injectable enalaprilat**, ACE inhibitors are **prodrugs** that require activation by **hepatic enzymes**.

Renal elimination 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. (**potassium supplements ?, potassium-sparing diuretics?**)

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 pregnancy.

2. Angiotensin receptor blockers

ARBs are **orally active compounds** that are **competitive antagonists** of the **angiotensin II type 1 receptor**.

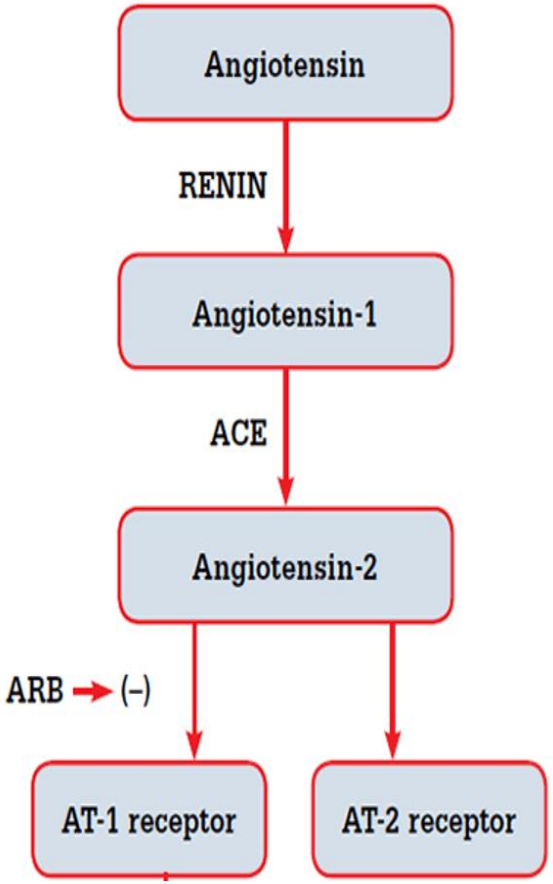
However, ARBs do **not affect bradykinin** levels.

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**.

Like ACE inhibitors, ARBs are **contraindicated** in **pregnancy**



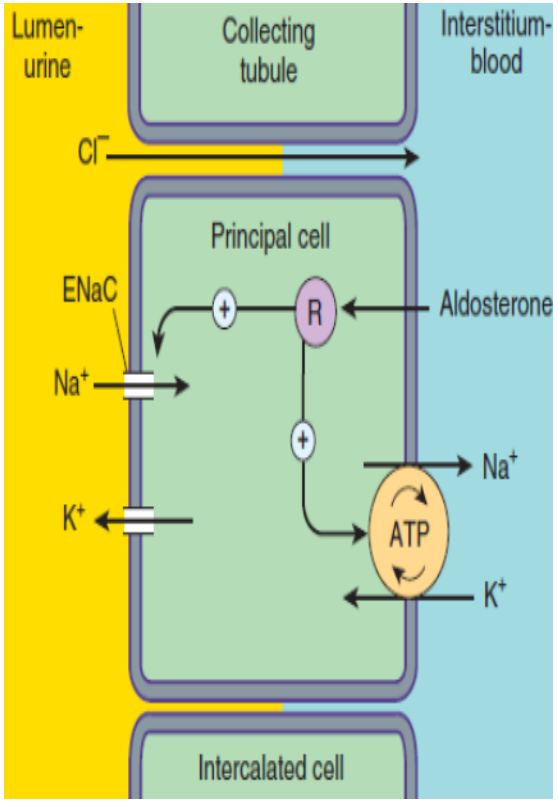
3. Aldosterone receptor antagonists

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** thereby **decreasing blood pressure**.

Loop diuretics are the most **commonly** used diuretics in HF.

Diuretics have **not been shown to improve survival** in HF.

6. ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI)

Sacubitril/valsartan combines the actions of an **ARB with neprilysin inhibition**.

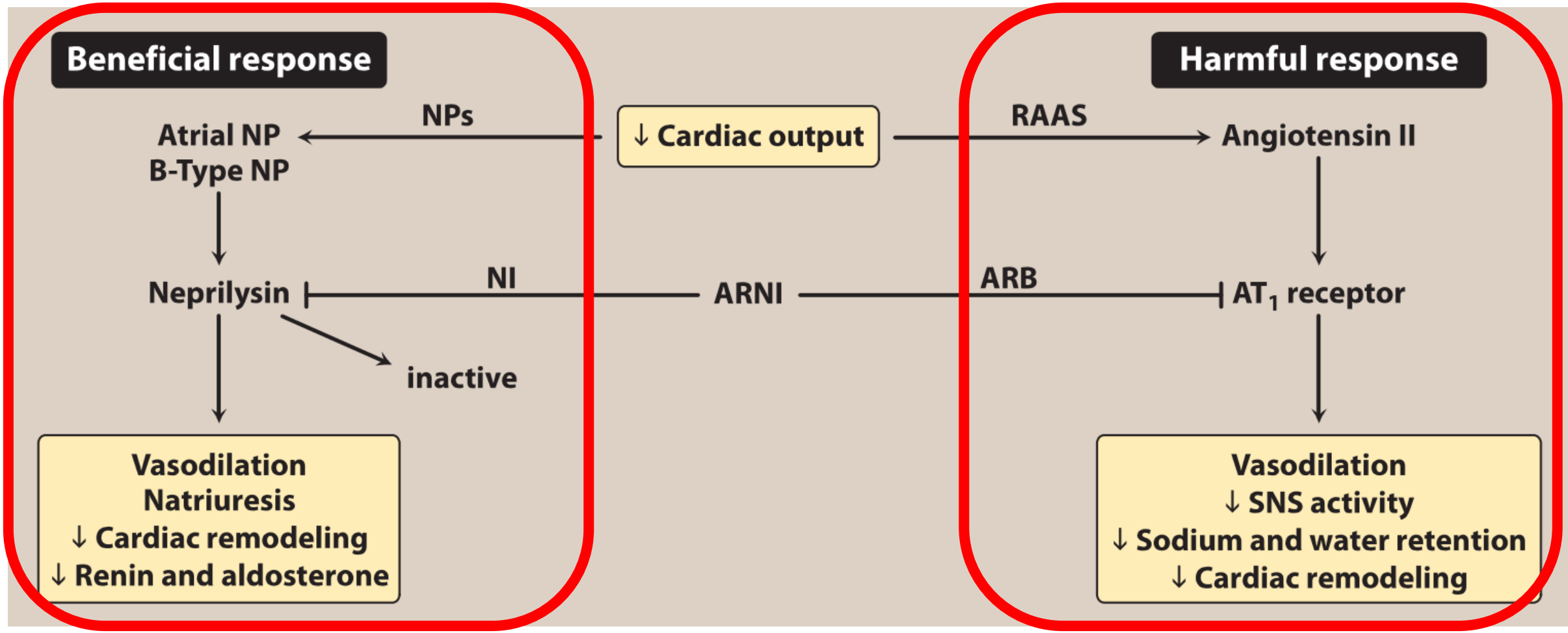
Inhibition of neprilysin results in **increased concentration of vasoactive peptides**, leading to **natriuresis, diuresis, vasodilation, and inhibition of fibrosis**.

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 inhibitors or ARBs 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 (ARNI)



7. HCN-GATED CHANNEL BLOCKER

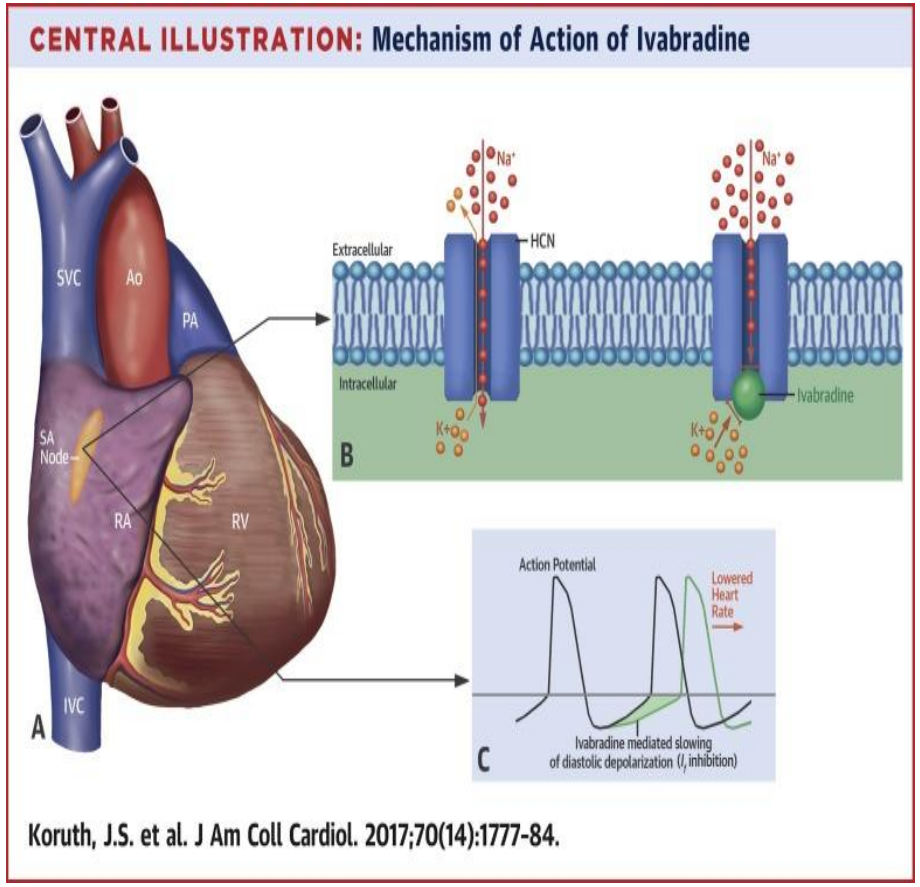
The hyperpolarization-activated cyclic nucleotide-gated (HCN) channel is responsible for the **I_f current and setting the pace within the SA node**.

Inhibition of the HCN channel results in **slowing of depolarization and a lower heart rate without a reduction in contractility, AV conduction, ventricular repolarization, or blood pressure**

Ivabradine is the only approved drug in the class of **HCN channel blockers**.

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 MEDICATIONS

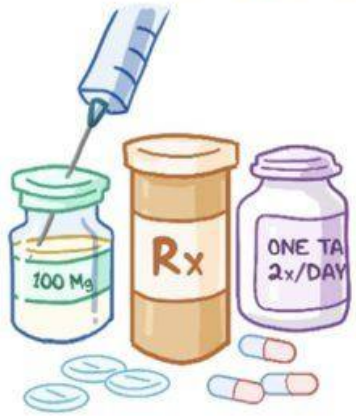
↑ STRENGTH of HEART MUSCLE CONTRACTION

↓

↑ STROKE VOLUME

↓

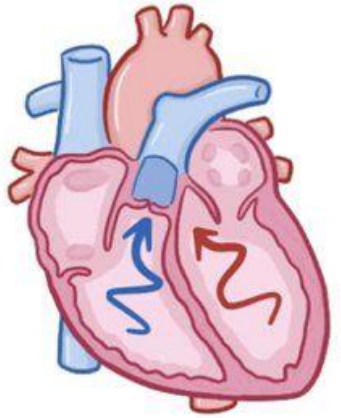
↑ CARDIAC OUTPUT



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

(e.g. systolic heart failure)

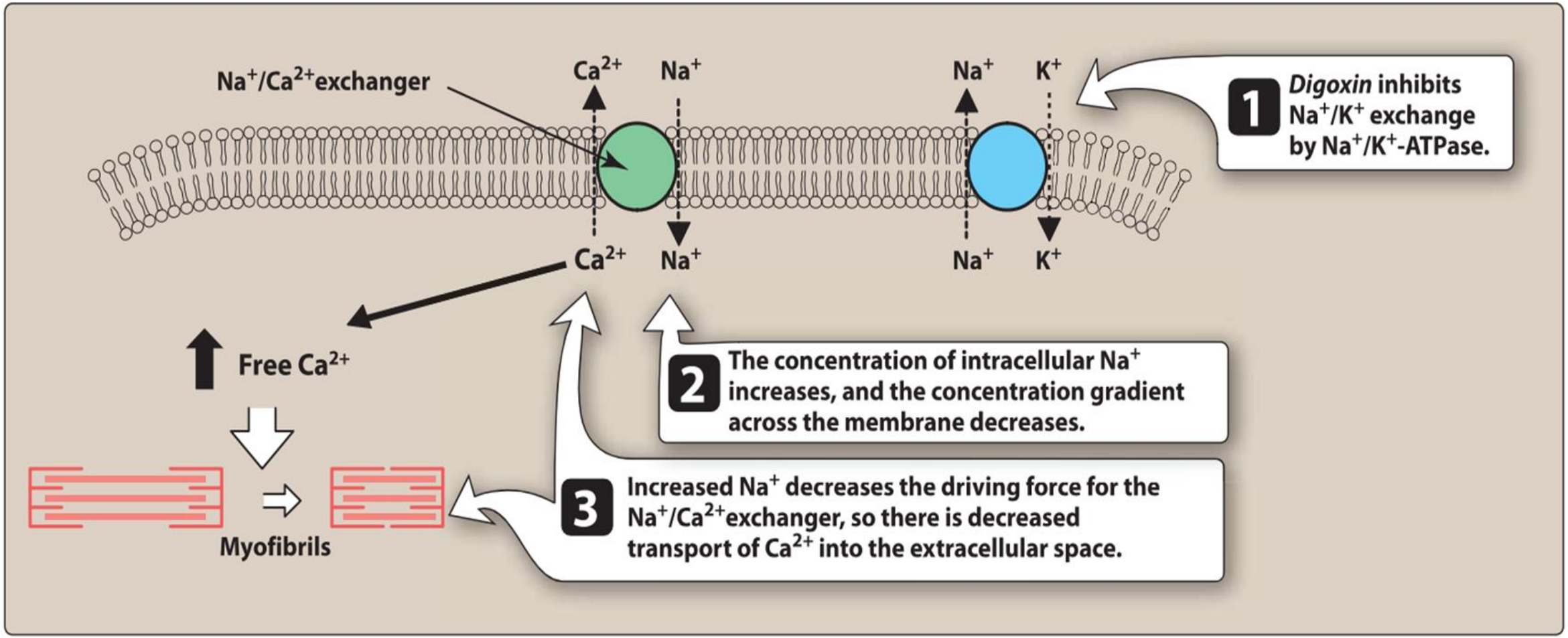
* CARDIAC GLYCOSIDES (e.g. digoxin)
* BETA AGONISTS (e.g. dobutamine)
* PHOSPHODIESTERASE INHBITORS (e.g. milrinone)



9. INOTROPIC DRUGS

	The digitalis glycosides have a **low therapeutic index.**
A. Digitalis glycosides (digoxin)	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 increase in free Ca^{2+},** 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**.

9. INOTROPIC DRUGS



Digitalis glycosides (digoxin) Mechanism of Action

9. INOTROPIC DRUGS

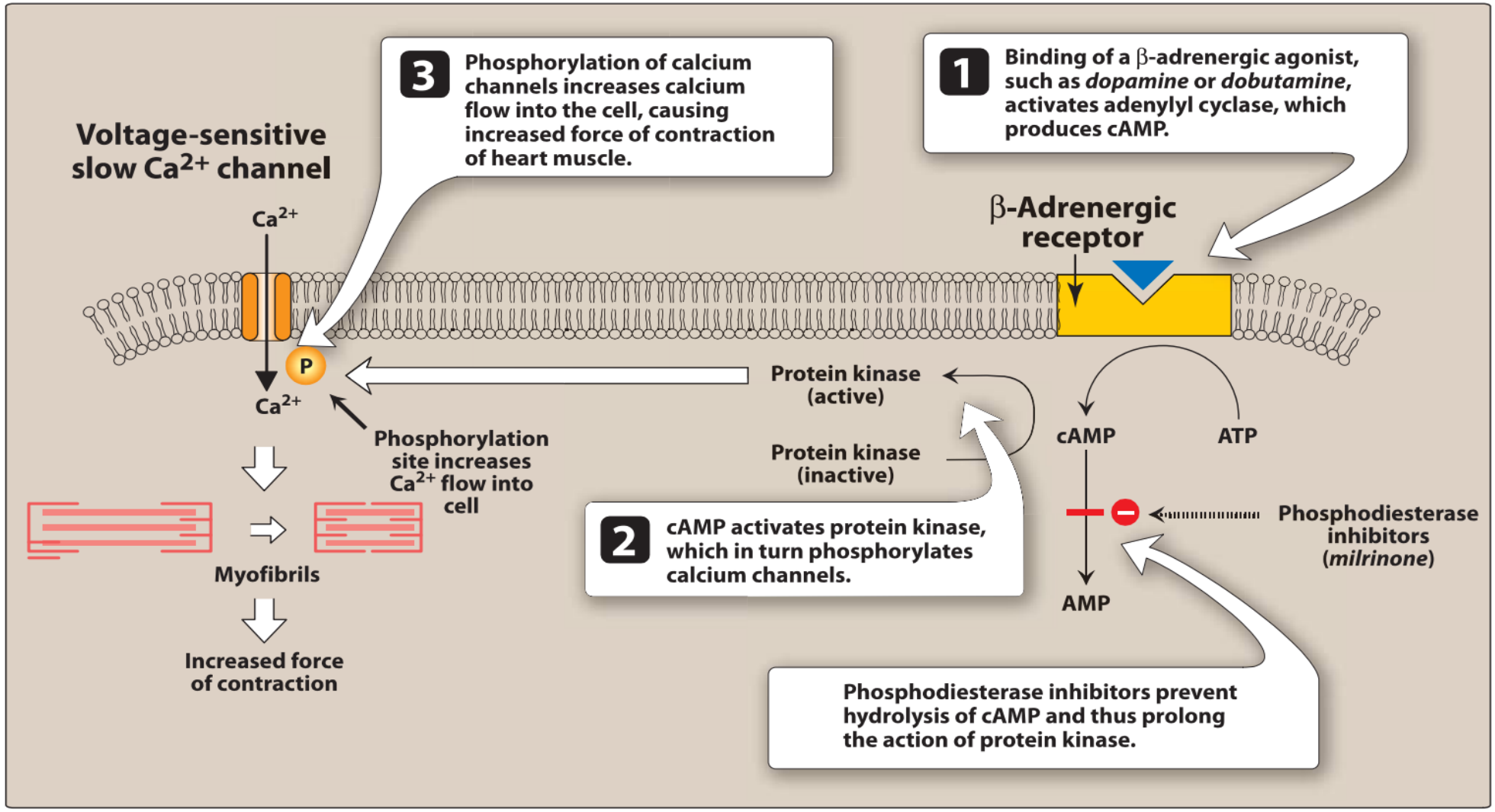
B. Beta-Adrenergic agonists:

- Beta-adrenergic agonists, such as **dobutamine and dopamine improve** cardiac performance by causing **positive inotropic effects and vasodilation**.
- Both drugs must be given by **intravenous infusion** and are primarily used in the **short-term** treatment of **acute HF in the hospital setting**.

C. 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**.

9. INOTROPIC DRUGS



Beta-Adrenergic agonists & Phosphodiesterase inhibitors Mechanism of Action

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

Loop Diuretics

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 Is ARBs

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

Beta blockers

Historically, **beta-blockers** were **added after** optimization of ACE inhibitor or ARB therapy;

ACE IS Beta blockers

However, most patients **newly diagnosed with HFrEF** are **initiated** on **both** low doses of an ACE inhibitor and beta-blocker **after initial stabilization**.

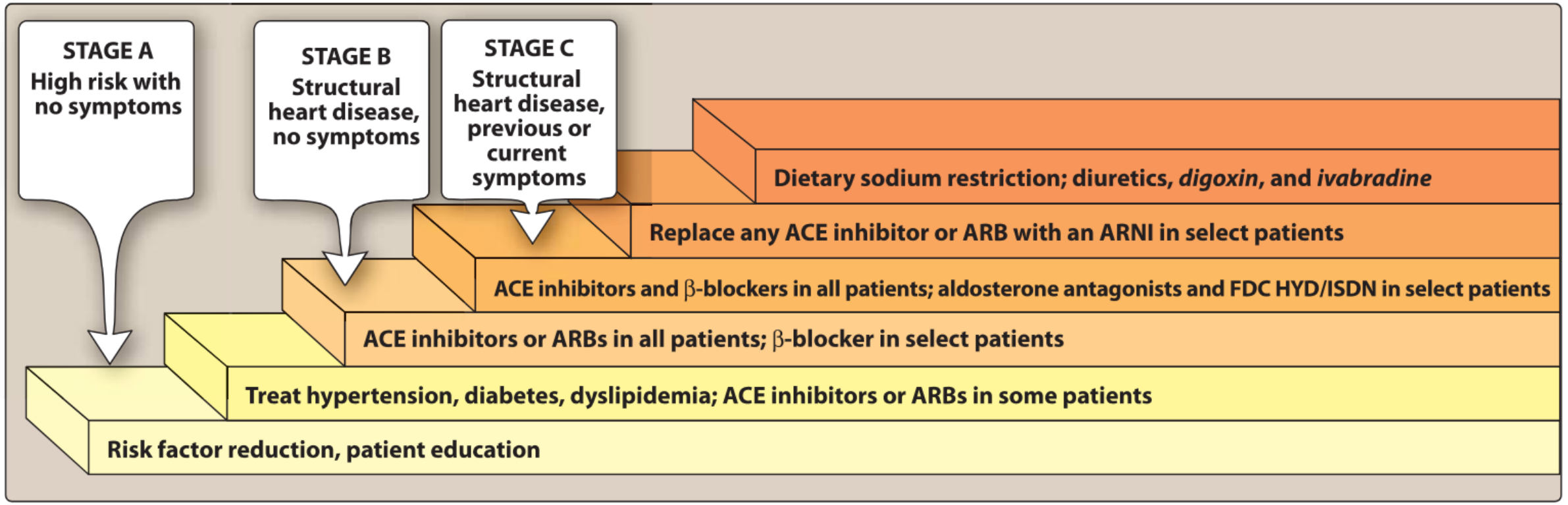
Aldosterone antagonists

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.

Digoxin Ivabradine

Lastly, **digoxin and ivabradine** are added for **symptomatic benefit only** in patients on optimal HF pharmacotherapy.

ORDER OF THERAPY



Thank You