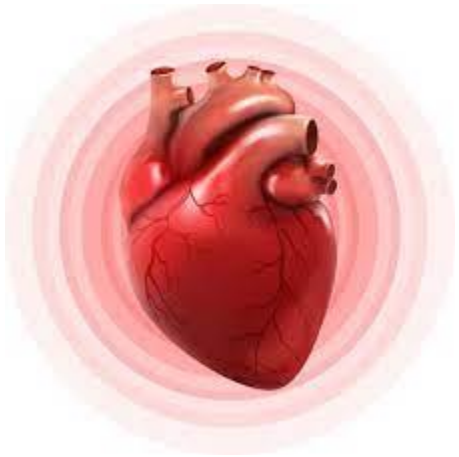
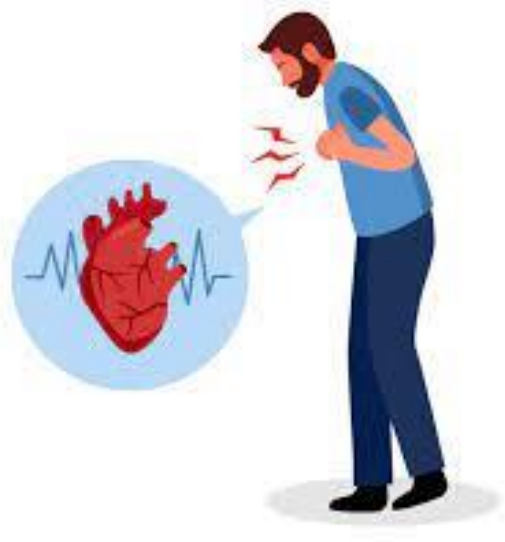
Mustansiriyah University
College of Pharmacy
Depart. of Pharmacology and Toxicology

Drugs for Heart Failure





Pharmacology 4th Stage

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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.

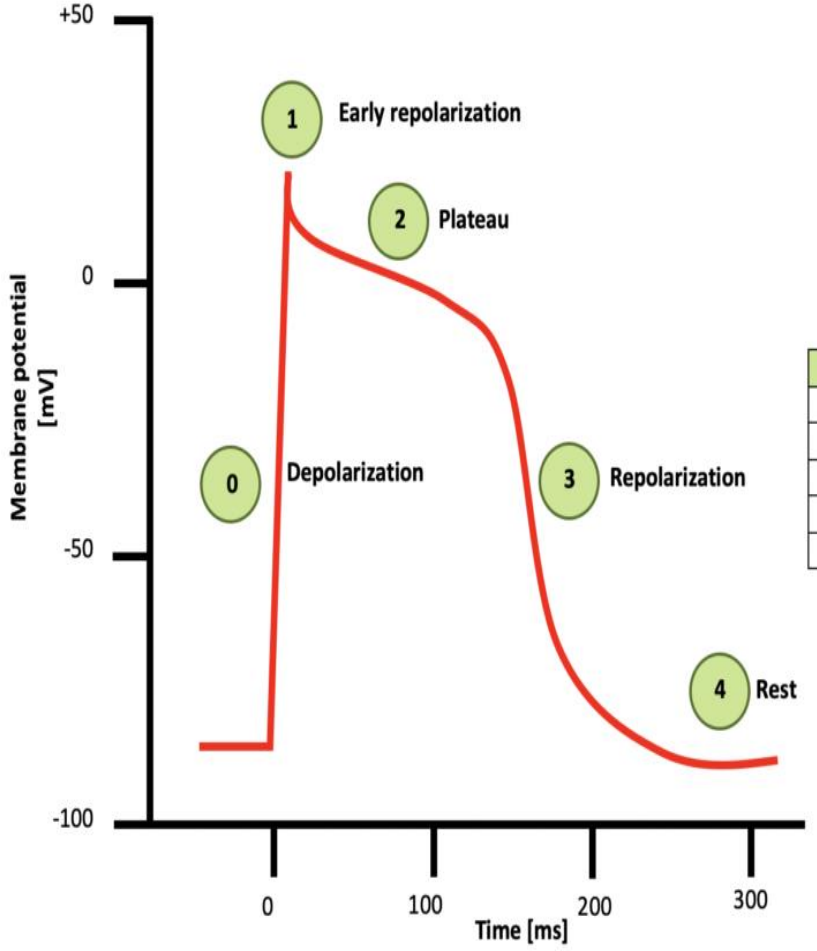
- HF causes include, but are not limited to, atherosclerotic heart disease, hypertensive heart disease, valvular heart disease, and congenital heart disease.

- Physiologic compensatory mechanisms can worsen the progression of HF.

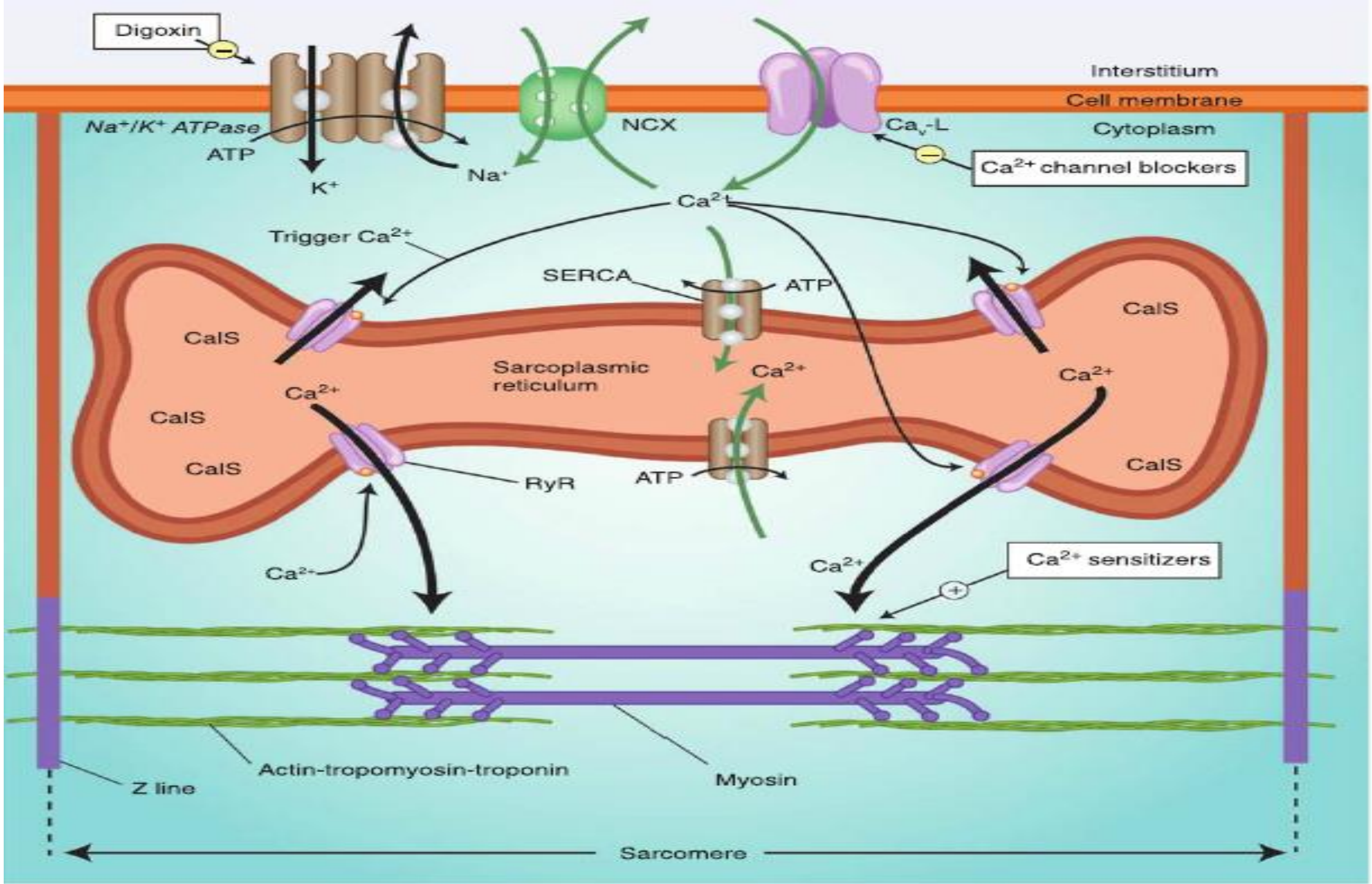
Physiology of Muscle Contraction

- Cardiac myocytes are electrically excitable and have a spontaneous, intrinsic rhythm generated by specialized "pacemaker" cells located in the sinoatrial (SA) and atrioventricular (AV) nodes.

- Cardiac myocytes also have an unusually long action potential, which can be divided into five phases (0 to 4).



Phase	Membrane channels
0	Na^+ open
1	Na^+ close
2	Ca^{2+} open; fast K^+ close
3	Ca^{2+} close; slow K^+ open
4	Resting potential

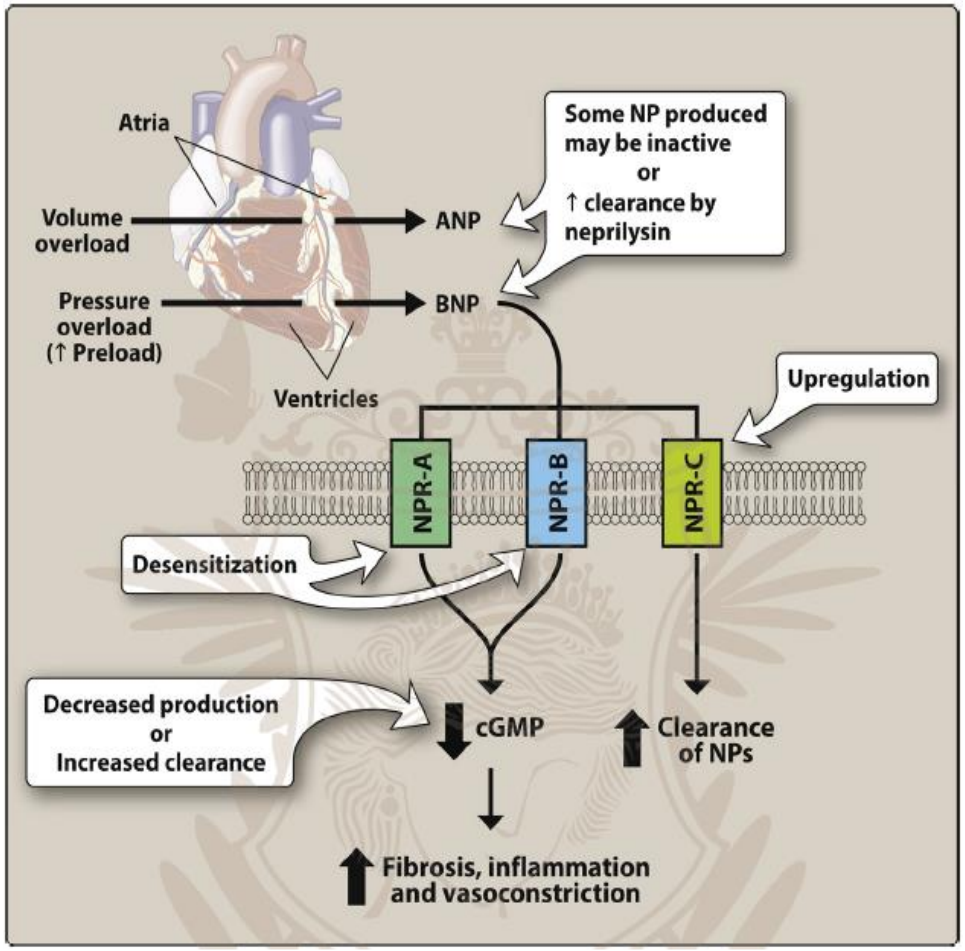

Digoxin
Interstitium
Cell membrane
Cytoplasm
Na+/K+ ATPase
ATP
K+
Na+
NCX
CaV-L
Ca2+ channel blockers
Ca2+
Trigger Ca2+
SERCA
ATP
CaIS
CaIS
CaIS
CaIS
CaIS
Sarcoplasmic reticulum
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
RyR
ATP
Ca2+ sensitizers
Actin-tropomyosin-troponin
Myosin
Z line
Sarcomere

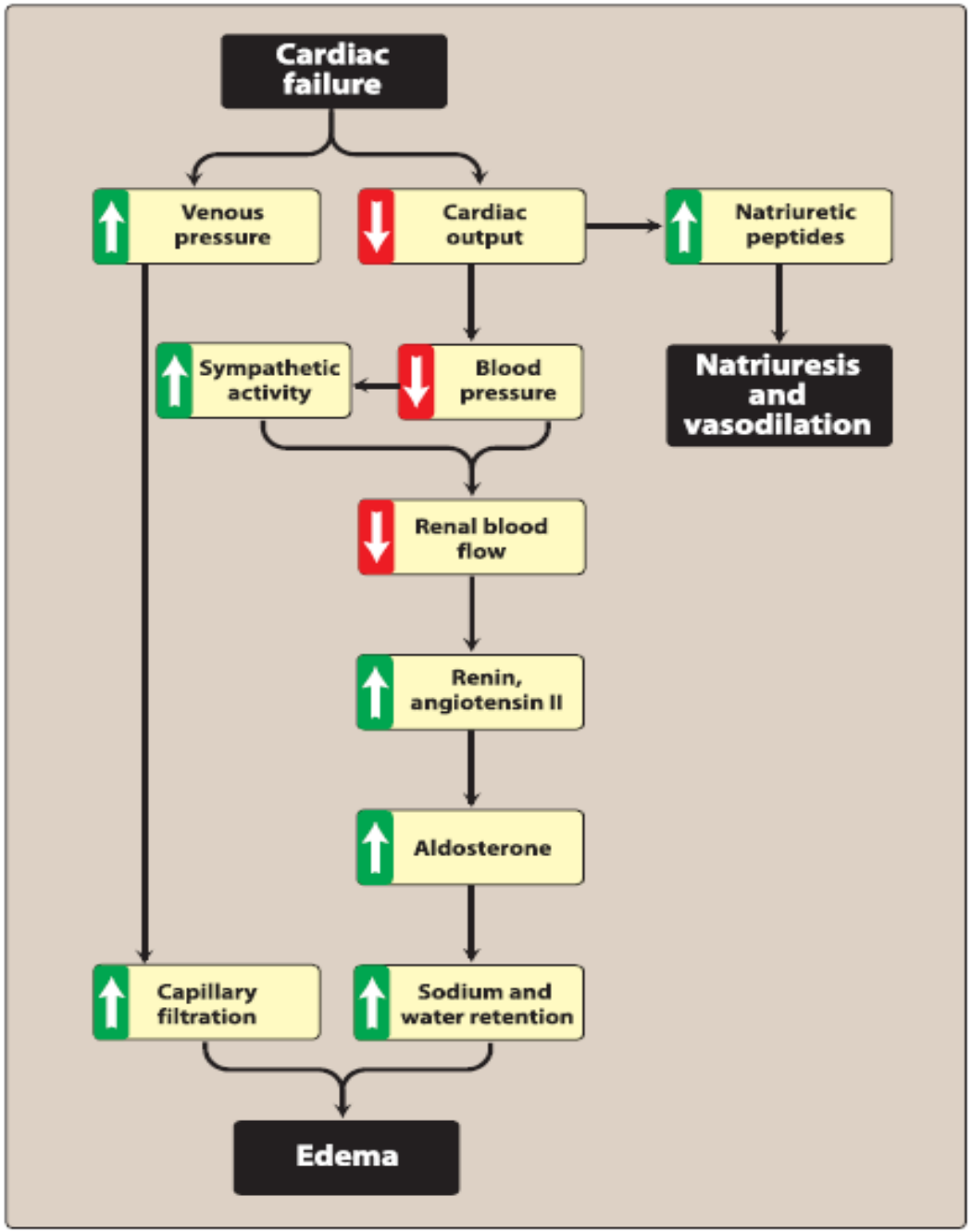
Compensatory physiological responses In HF

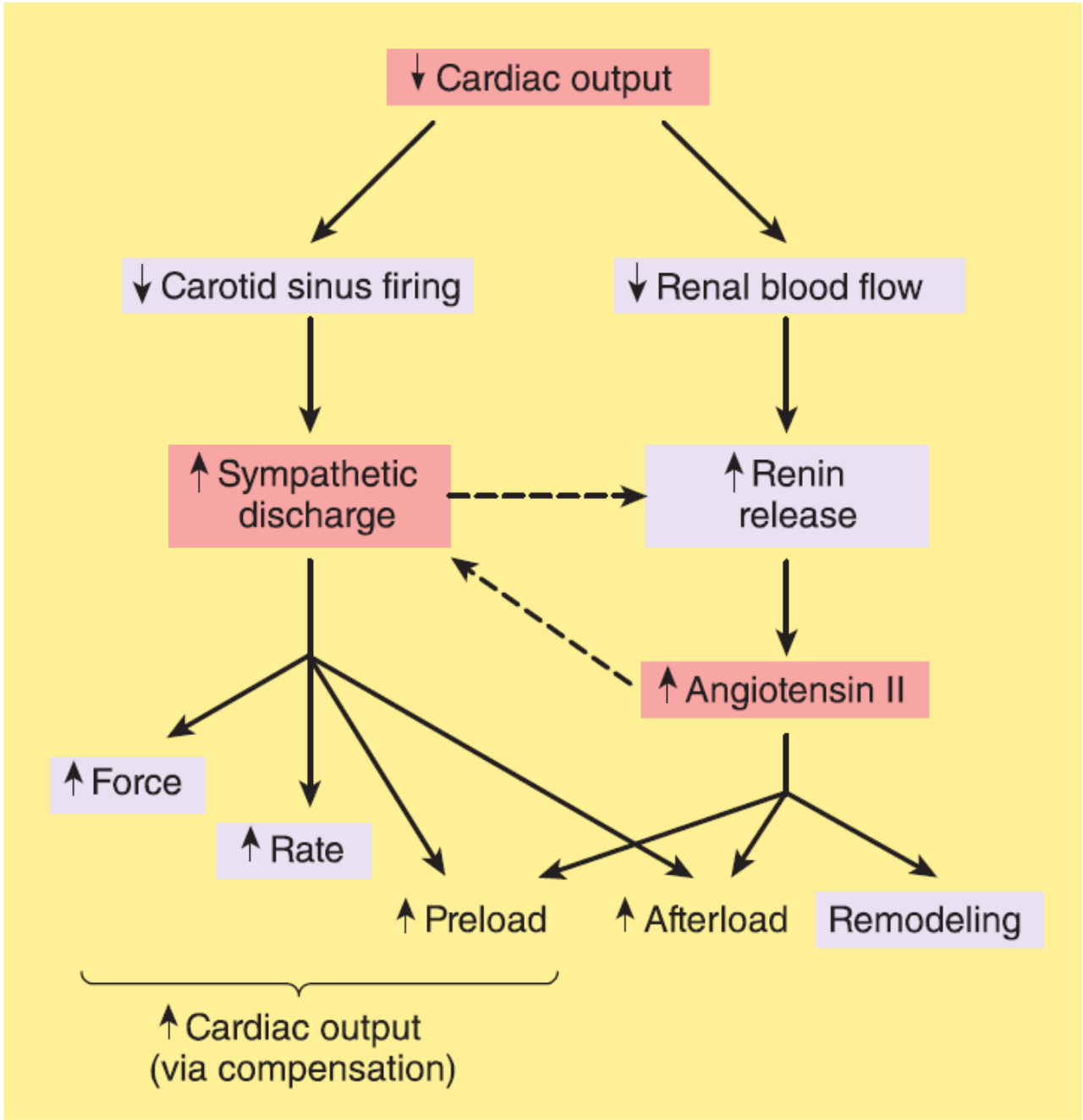
1. Increased sympathetic activity: Baroreceptors sense a decrease in blood pressure and activate the sympathetic nervous system.
2. Activation of the renin-angiotensin-aldosterone system (RAAS): A fall in cardiac output decreases blood flow to the kidney, prompting the release of renin.
3. Activation of natriuretic peptides: Activation of the natriuretic peptides due to increase preload ultimately results in vasodilation, natriuresis, inhibition of renin and aldosterone release, and a reduction in myocardial fibrosis.
4. Myocardial hypertrophy: excessive elongation of the fibers results in weaker contractions and a diminished ability to eject blood. "systolic failure" or HF with reduced ejection fraction (HFrEF). (HFpEF).???

Compensatory physiological responses In HF

5. Increased inflammation and oxidative stress: HFrEF leads to tissue hypoperfusion, neurohormonal activation, and volume overload. These, along with impaired cardiac energy metabolism, contribute to mitochondrial dysfunction, oxidative stress, and inflammation. The result in either HFrEF or HFpEF is impaired calcium regulation, cardiac hypertrophy, and cardiac myocyte death and fibrosis.
6. Resistance to natriuretic peptides: The potential mechanisms for resistance to natriuretic peptides are prereceptor-, receptor-, or postreceptor mediated.




Cardiac failure
Venous pressure
Cardiac output
Natriuretic peptides
Sympathetic activity
Blood pressure
Natriuresis and vasodilation
Renal blood flow
Renin, angiotensin II
Aldosterone
Capillary filtration
Sodium and water retention
Edema


↓ Cardiac output
↓ Carotid sinus firing
↓ Renal blood flow
↑ Sympathetic discharge
↑ Renin release
↑ Angiotensin II
↑ Force
↑ Rate
↑ Preload
↑ Afterload
Remodeling
↑ Cardiac output (via compensation)

Therapeutic strategies in HF

- Fluid limitations
- low dietary intake of sodium
- Treatment of comorbid conditions
- Using HF drugs
- Avoid drugs that may precipitate or exacerbate HF
  - NSAID
  - Alcohol
  - nondihydropyridine calcium channel blockers
  - some antiarrhythmic drugs

- Goals of treatment are to

1. alleviate symptoms
2. slow disease progression
3. improve survival.

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

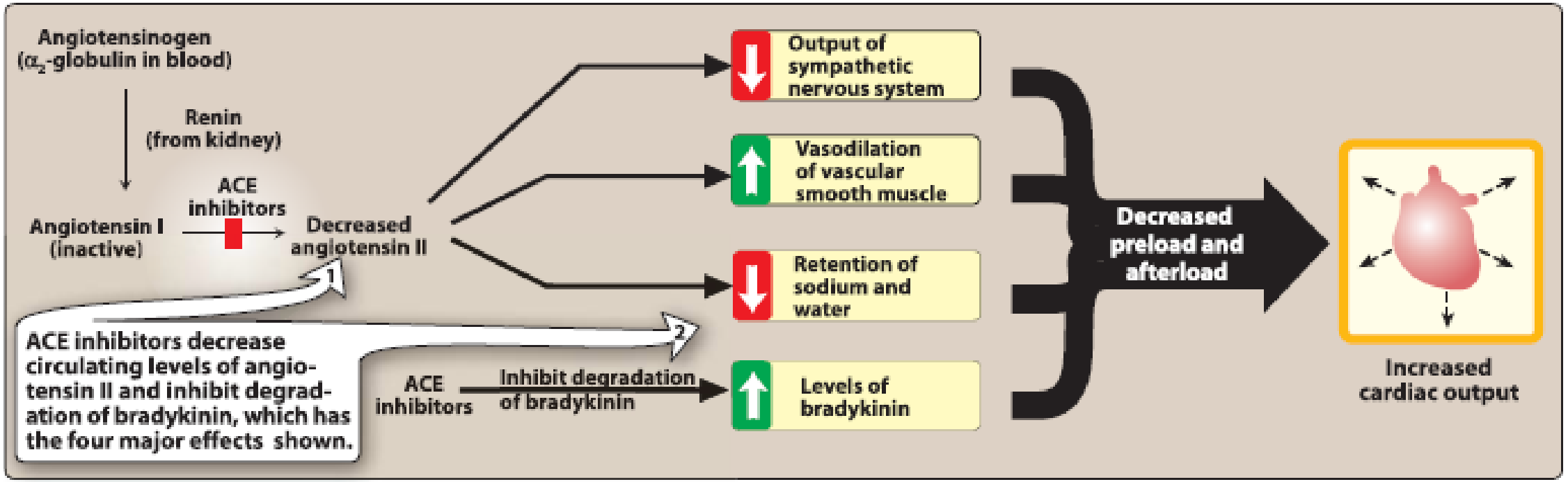
Digoxin LANOXIN
Dobutamine DOBUTREX
Dopamine GENERIC ONLY
Milrinone GENERIC ONLY

B-TYPE NATRIURETIC PEPTIDE

Nesiritide NATRECOR

Inhibitor of RAAS: 1- ACEI

- 1. Actions: Angiotensin-converting enzyme inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output and improve patient survival in HF.
- Therapeutic use: asymptomatic and symptomatic HFrEF.



I- Inhibitor of RAAS: **1- ACEI** Cont..

- Pharmacokinetics: prodrug? Liver and kidney excretion ?
- Adverse effects: postural hypotension, renal insufficiency, hyperkalemia!!, a persistent dry cough!!, and angioedema (rare).
- Serum creatinine levels should be monitored ??

Inhibitor of RAAS: 2- ARBs

- Action: Although ARBs have a different mechanism of action than ACE inhibitors, their actions on preload and afterload are similar. However, ARBs do not affect bradykinin levels. How?

- Pharmacokinetics: plasma protein bound? first-pass hepatic Metabolism? Active or inactive metabolism? Excretion ?

- Adverse effects: same ACEI but the ARBs have a lower incidence of cough and angioedema

Inhibitor of RAAS: 3- Aldosterone (mineralocorticoid) receptor antagonist

- Patients with HF have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone.
- Spironolactone and eplerenone preventing salt retention, myocardial hypertrophy, and hypokalemia . Spironolactone also has affinity for androgen and progesterone receptors and may cause gynecomastia and dysmenorrhea.
- Aldosterone antagonists are indicated in patient with HFrEF or HFrEF and recent myocardial infarction.

4- β-Blockers

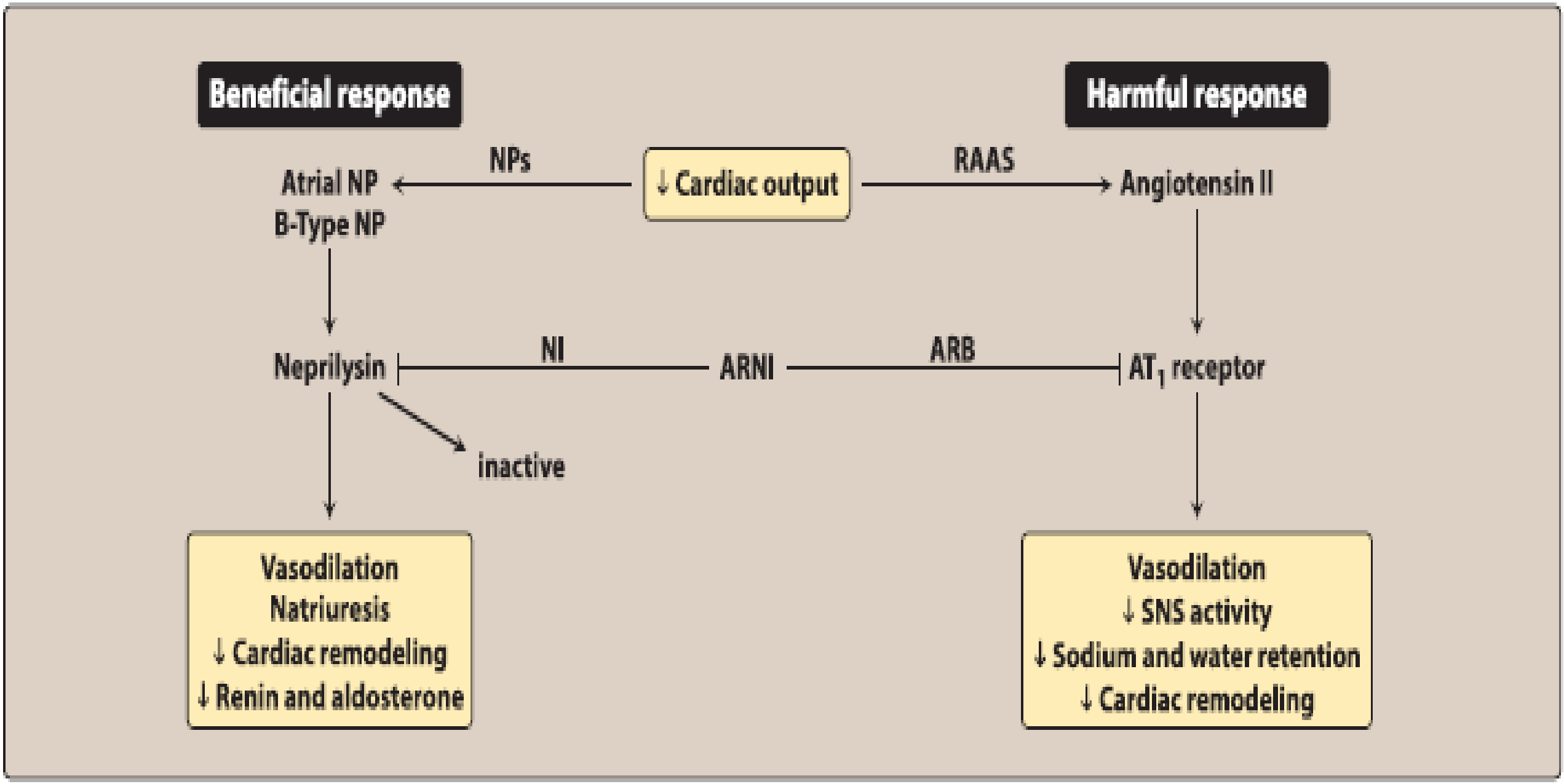
- β-Blockers have negative inotropic activity in HF!!!! And used in HFrEF
- These agents decrease heart rate and inhibit release of renin in the kidneys prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.
- Bisoprolol, carvedilol and long-acting metoprolol succinate.
- Pharmacokinetics: start low dose then titrate!! cytochrome P450? P-glycoprotein (P-gp) ??? Caution?

5- Diuretics

- Diuretics reduce signs and symptoms of volume overload, such as dyspnea on exertion, orthopnea, and peripheral edema. This decreases cardiac workload and oxygen demand
- 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.
- they should only be used to treat signs and symptoms of volume excess

6- angiotensin receptor -neprilysin inhibitors (ARNI)

- ARBs not ACEI used. Why?
- Sacubitril/valsartan
  - Actions: the combination decreases afterload, preload, and myocardial fibrosis.
  - Therapeutic use: ARNI should replace an ACE inhibitor or ARB in patients with HFrEF who remain symptomatic on optimal doses of a β-blocker and an ACE inhibitor or ARB.
  - PK: prodrug? Excretion ?
  - Adverse effects: hypotension, bradykinin levels may increase and angioedema may occur.
  - Caution and contraindication: ??

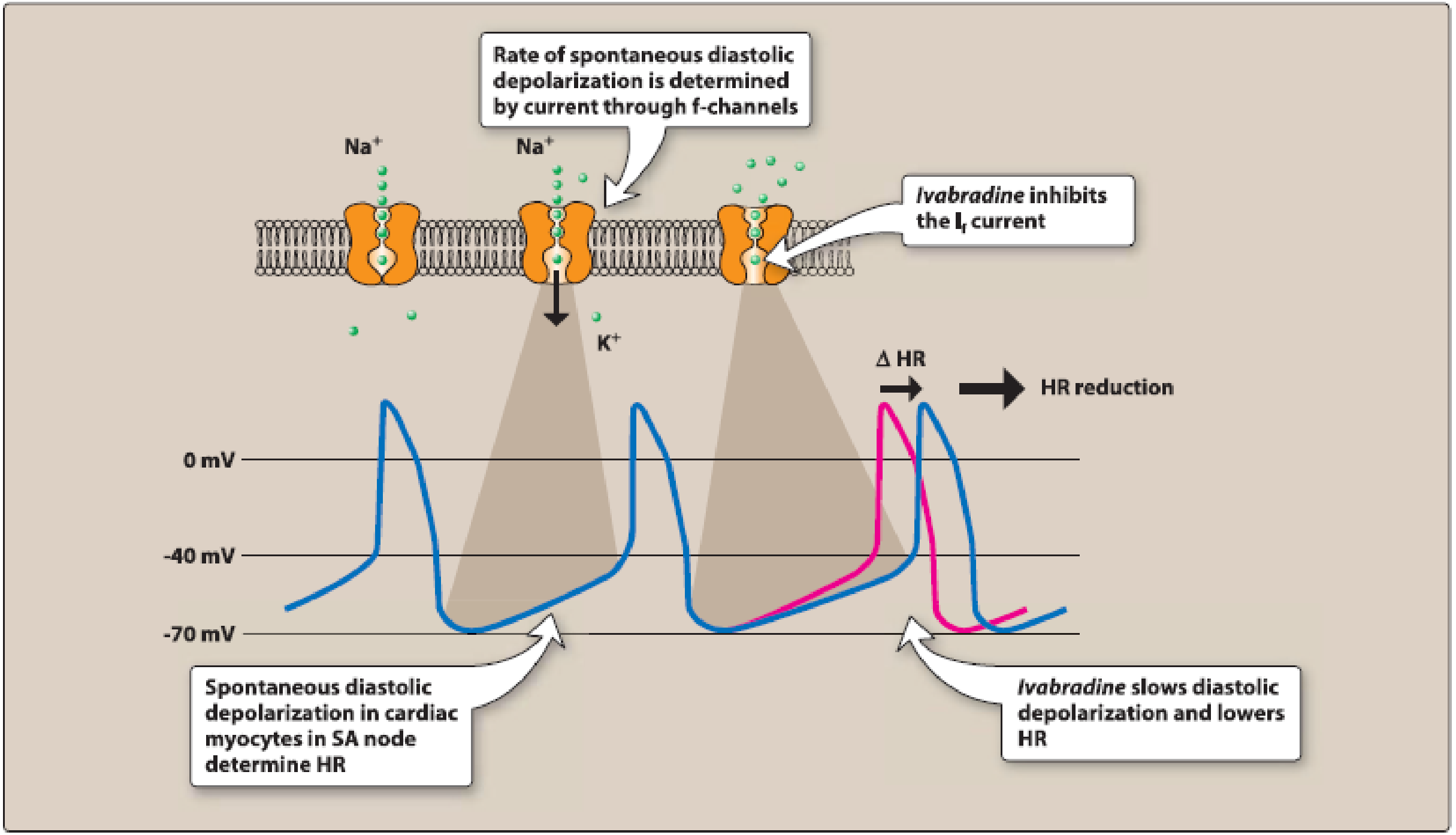

Beneficial response
Harmful response
NPs
RAAS
Atrial NP
B-Type NP
↓ Cardiac output
Angiotensin II
Neprilysin
NI
ARNI
ARB
AT1 receptor
inactive
Vasodilation
Natriuresis
↓ Cardiac remodeling
↓ Renin and aldosterone
Vasodilation
↓ SNS activity
↓ Sodium and water retention
↓ Cardiac remodeling

7- hyperpolarization-activated cyclic nucleotide-gated (HCN) channel

- Ivabradine

selectively slowing the If 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.

- PK: cytochrome P450 3A4? Active metabolites?
- Adverse effects: Bradycardia, atrial fibrillation, luminous phenomena,
- Caution: β-Blockers ? advanced heart block, or with potent 3A4 inhibitors? .

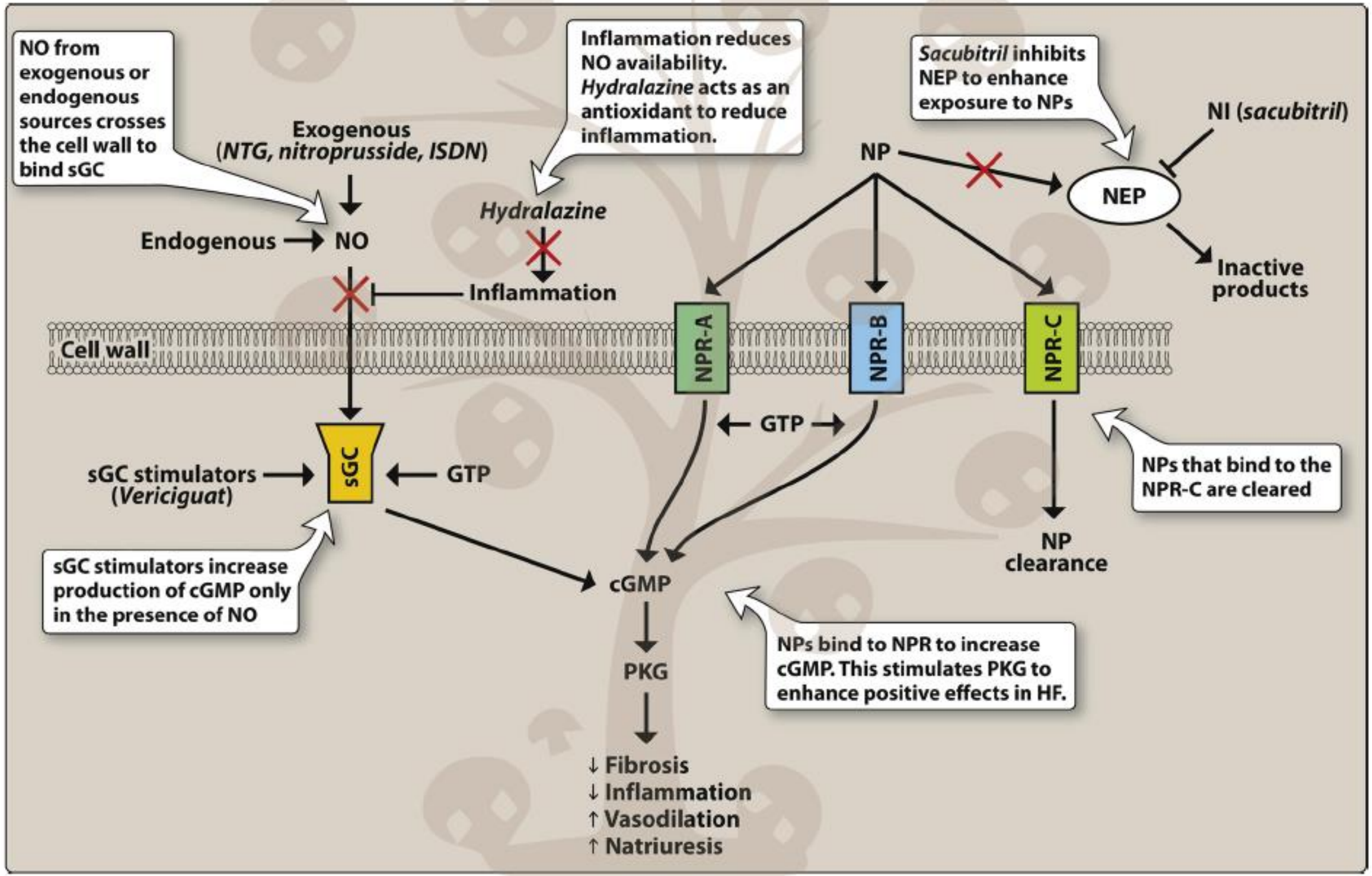

Rate of spontaneous diastolic depolarization is determined by current through f-channels
Na+
Na+
Ivabradine inhibits the If current
K+
Δ HR
HR reduction
0 mV
-40 mV
-70 mV
Spontaneous diastolic depolarization in cardiac myocytes in SA node determine HR
Ivabradine slows diastolic depolarization and lowers HR

8- Vasodilators

- **A. Arterial vasodilators: Hydralazine**

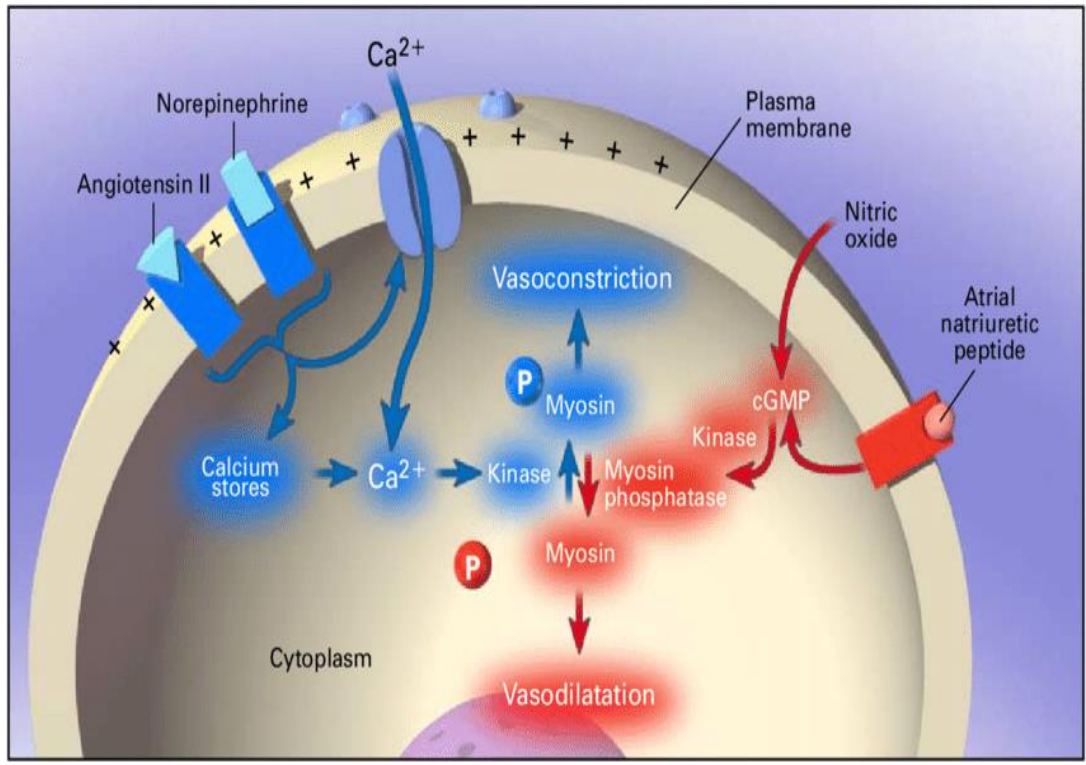
reduce afterload and is most often used in combination with an oral nitrate in chronic HF.

- **MOA**: it is thought to reduce calcium in arteriole smooth muscle leading to vasodilation, afterload reduction, and increased cardiac output. Hydralazine also possesses antioxidant properties. Inhibiting oxidases prevents the breakdown of endogenous and exogenous nitric oxide (NO). Enhancing nitric oxide results in vasodilation and reduction in afterload and preload
- **PK**: oral, IV, IM, 90% bioavailability, take without food, short acting.
- **Adverse effects:** Headache, dizziness, hypotension, reflex tachycardia, and edema!!!! , lupus (rare)


NO from exogenous or endogenous sources crosses the cell wall to bind sGC
Exogenous (NTG, nitroprusside, ISDN)
Endogenous
NO
Inflammation reduces NO availability. Hydralazine acts as an antioxidant to reduce inflammation.
Hydralazine
Inflammation
Sacubitril inhibits NEP to enhance exposure to NPs
NI (sacubitril)
NP
NEP
Inactive products
Cell wall
NPR-A
NPR-B
NPR-C
GTP
sGC stimulators (Vericiguat)
sGC
GTP
sGC stimulators increase production of cGMP only in the presence of NO
NPs that bind to the NPR-C are cleared
NP clearance
cGMP
PKG
NPs bind to NPR to increase cGMP. This stimulates PKG to enhance positive effects in HF.
↓ Fibrosis
↓ Inflammation
↑ Vasodilation
↑ Natriuresis

8- Vasodilators Cont..

- **B- Arterial and venous dilators:**
  Nitrate, isosorbide dinitrate, nitroprusside
- **MOA:** quickly convert to NO and bind soluble guanylate cyclase (sGC). This activation increases intracellular cGMP in smooth muscle cells which activates protein kinase G (PKG) and ultimately results in producing vasodilation (decrease preload and afterload).
- **Uses**: in combination with hydralazine for African-Americans with HFrEF !!!!!?



8- Vasodilators Cont..

- **PK**: ISDN undergoes high first-pass metabolism to active metabolite ? Rapid onset 30 min and duration 4-6 hr. IV Nitroglycerin has high first-pass hepatic metabolism and periphery by transferases and esterases. Fast onset and 2-6min t1/2.

Nitroprusside dissociates upon contact with sulfhydryl groups found on all cell walls to iron NO and cyanide groups. It also dissociates when in contact with hemoglobin to form cyanmethemoglobin and cyanide. Cyanide reacts with thiosulfate to form thiocyanate to allow for renal excretion. cyanide toxicity ??

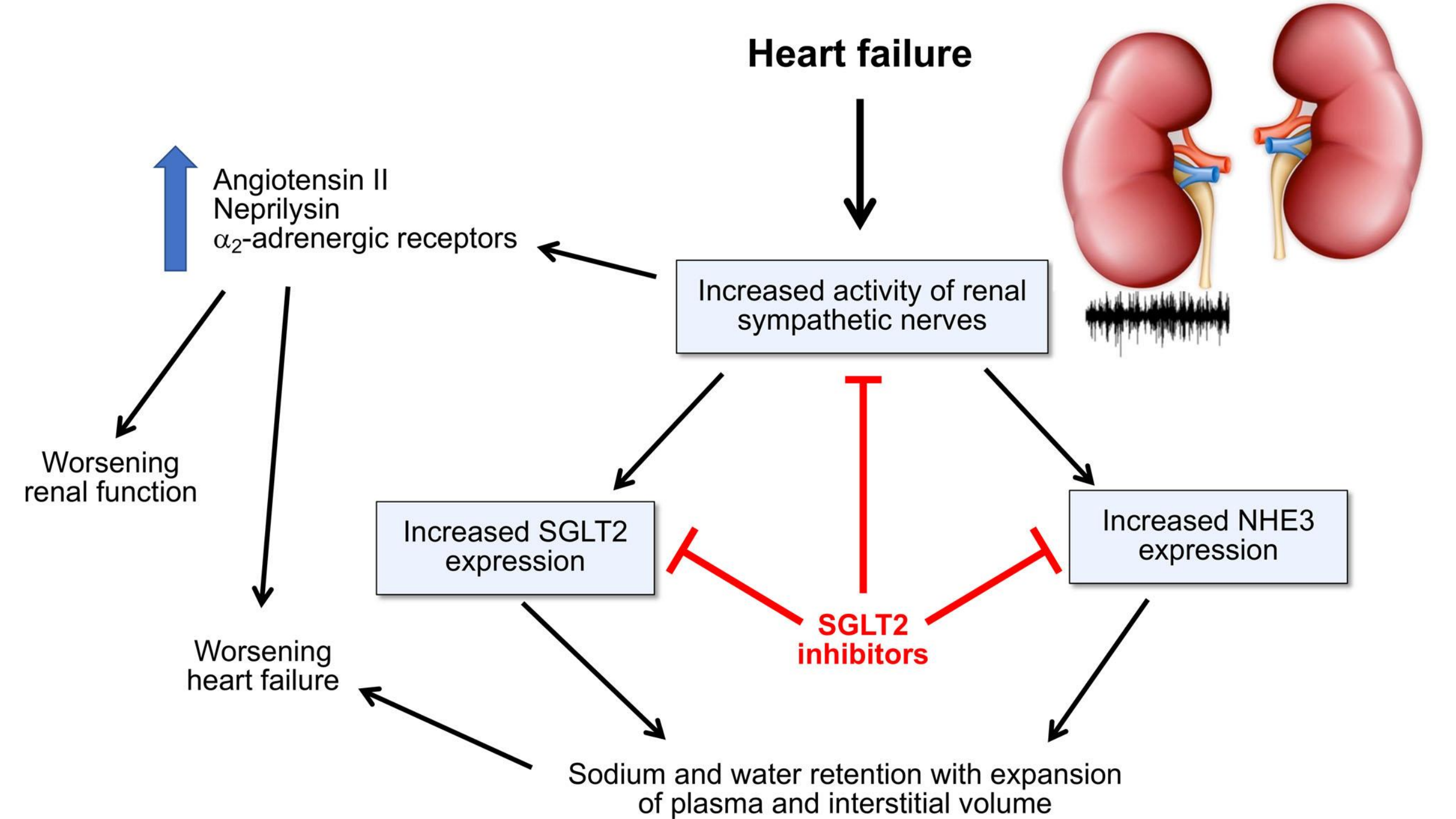
- **Adverse effects:** headache and dizziness can be dose limiting, hypotension , rarely cause methemoglobinemia. nitroprusside can cause cyanide toxicity.

9- Soluble Guanylate Cyclase stimulators

- **Vericiguat:** is a long-acting oral sGC stimulator
- **MOA**: Vericiguat directly stimulates sGC through a different binding site than NO and sensitizes sGC to endogenous NO and synthesize cGMP. An increase in cGMP activates PKG to ultimately improve left ventricular compliance, vasodilate, reduce inflammation, and prevent hypertrophy and fibrosis.
- **PK**: oral with food to increase bioavailability, t1/2 = 30 hr , once daily, primarily excreted in the urine as inactive metabolite and lesser extent as unchanged drug in feces.
- **Adverse effects**: Hypotension, syncope, and anemia. C.I in pregnancy (risk of cardiac malformations). Avoided with nitrates or phosphodiesterase inhibitors due to the risk of excessive hypotension.

10- **Sodium–glucose Cotransporter 2 Inhibitors (SGLT2i)**

- SGLT2 inhibitors (Dapagliflozin and empagliflozin) reduce plasma volume through glucosuria and natriuresis, thereby lowering preload and afterload. SGLT2 inhibitors may also increase cardiac efficiency by shifting energy metabolism toward oxidation of ketone bodies, reducing oxidative stress by inhibition of the myocardial sodium–hydrogen exchanger and preventing cardiac fibrosis through inhibition of myofibroblast differentiation.!!
- **MOA**: inhibit SGLT2 in the proximal tubule to reduce reabsorption of glucose and sodium resulting in glucosuria and natriuresis. Compared with diuretics, SGLT2 inhibitors may selectively reduce interstitial volume versus intravascular volume, thus limiting reflexive neurohormonal stimulation !!!


Heart failure
Angiotensin II
Neprilysin
α2-adrenergic receptors
Increased activity of renal sympathetic nerves
Worsening renal function
Increased SGLT2 expression
Increased NHE3 expression
SGLT2 inhibitors
Worsening heart failure
Sodium and water retention with expansion of plasma and interstitial volume

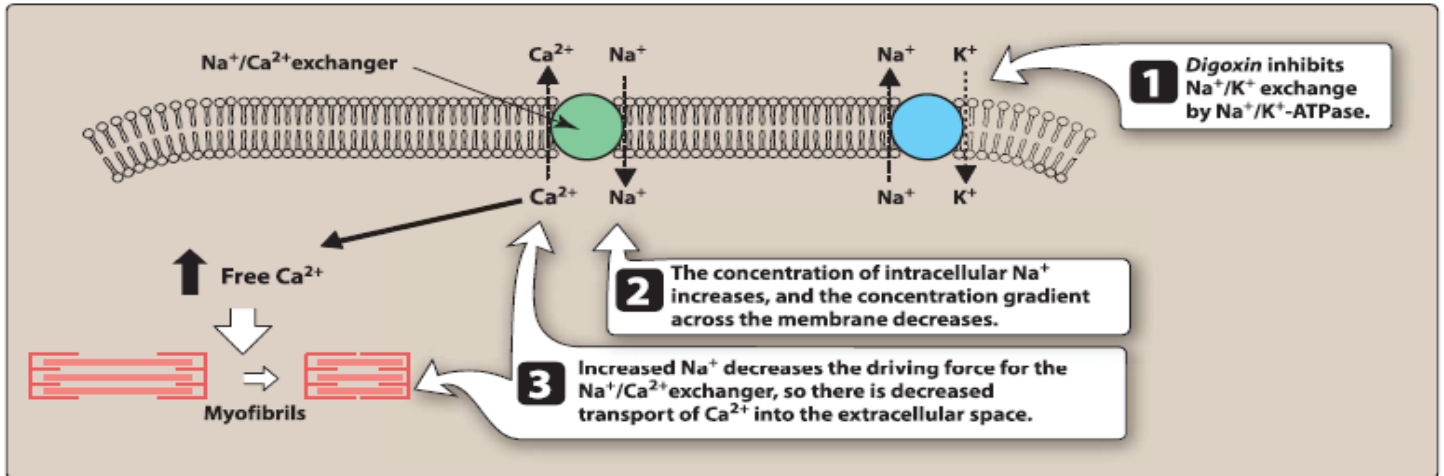
10- **SGLT2 inhibitors Cont..**

- **Uses**: symptomatic HFrEF who are on optimal HF pharmacotherapy with β-blockers, ACE inhibitors, and MRAs.
- **Pharmacokinetics**: Dapagliflozin and empagliflozin are well absorbed regardless food content . metabolized via glucuronidation. renally excreted, T1/2=12 hours, once-daily dosing.
- **Adverse effects:** volume depletion, renal insufficiency, and urogenital infections. hypoglycemia when combined with a sulfonylurea or insulin. Rare: diabetic ketoacidosis, Fournier gangrene, and bone fractures, may occur.

11- Inotropic Drugs: A- Digitalis glycosides

- Positive inotropic agents enhance cardiac contractility and, thus, increase cardiac output. The inotropic action is the result of an increased cytoplasmic calcium concentration
- **MOA**:

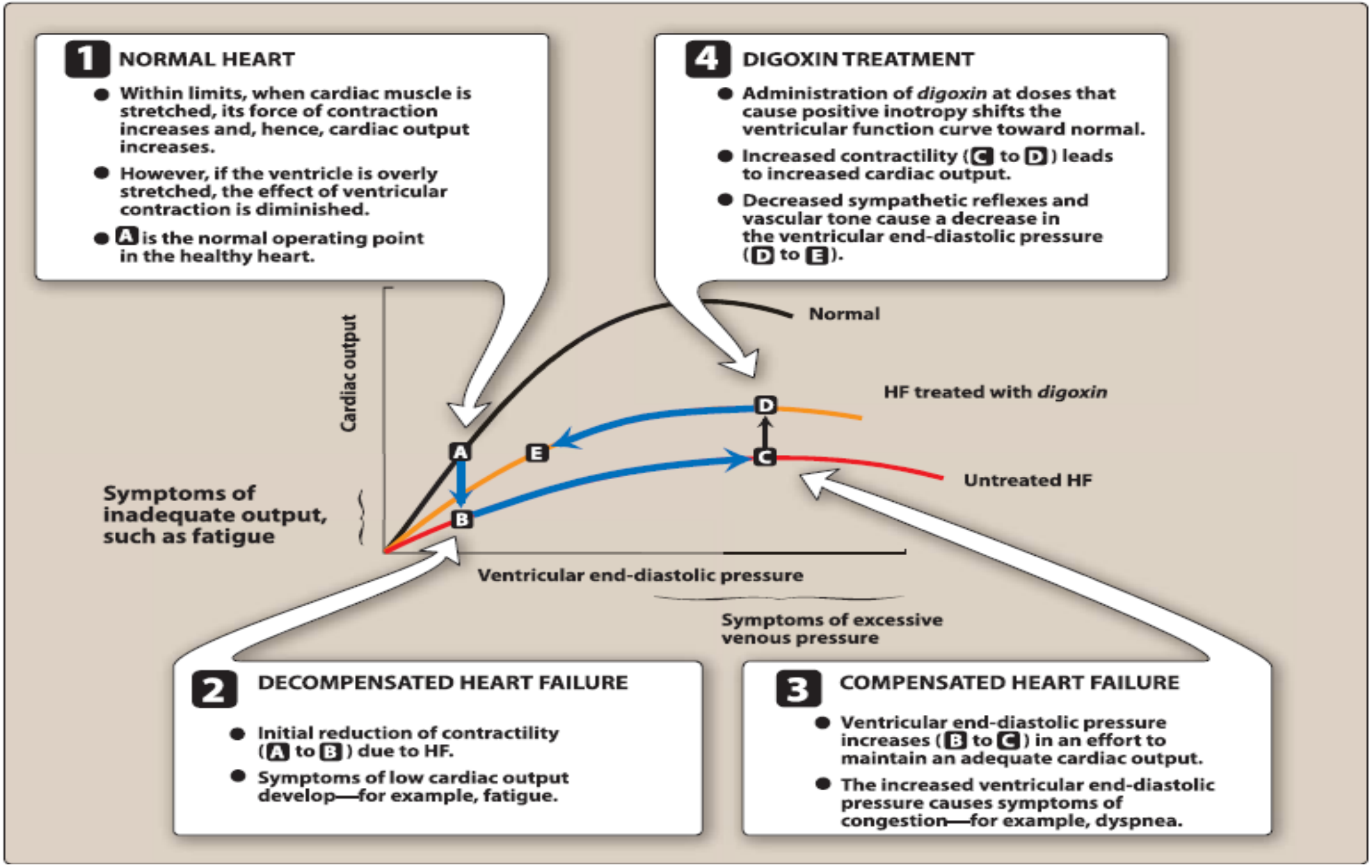
1. **Regulation of cytosolic calcium concentration**: By inhibiting the Na+/K+-ATPase enzyme, digoxin reduces the ability of the myocyte to actively pump Na+ from the cell. This ultimately results in a small but physiologically important increase in free Ca2+, thereby leading to increased cardiac contractility.



11- Inotropic Drugs: A- Digoxin Cont..

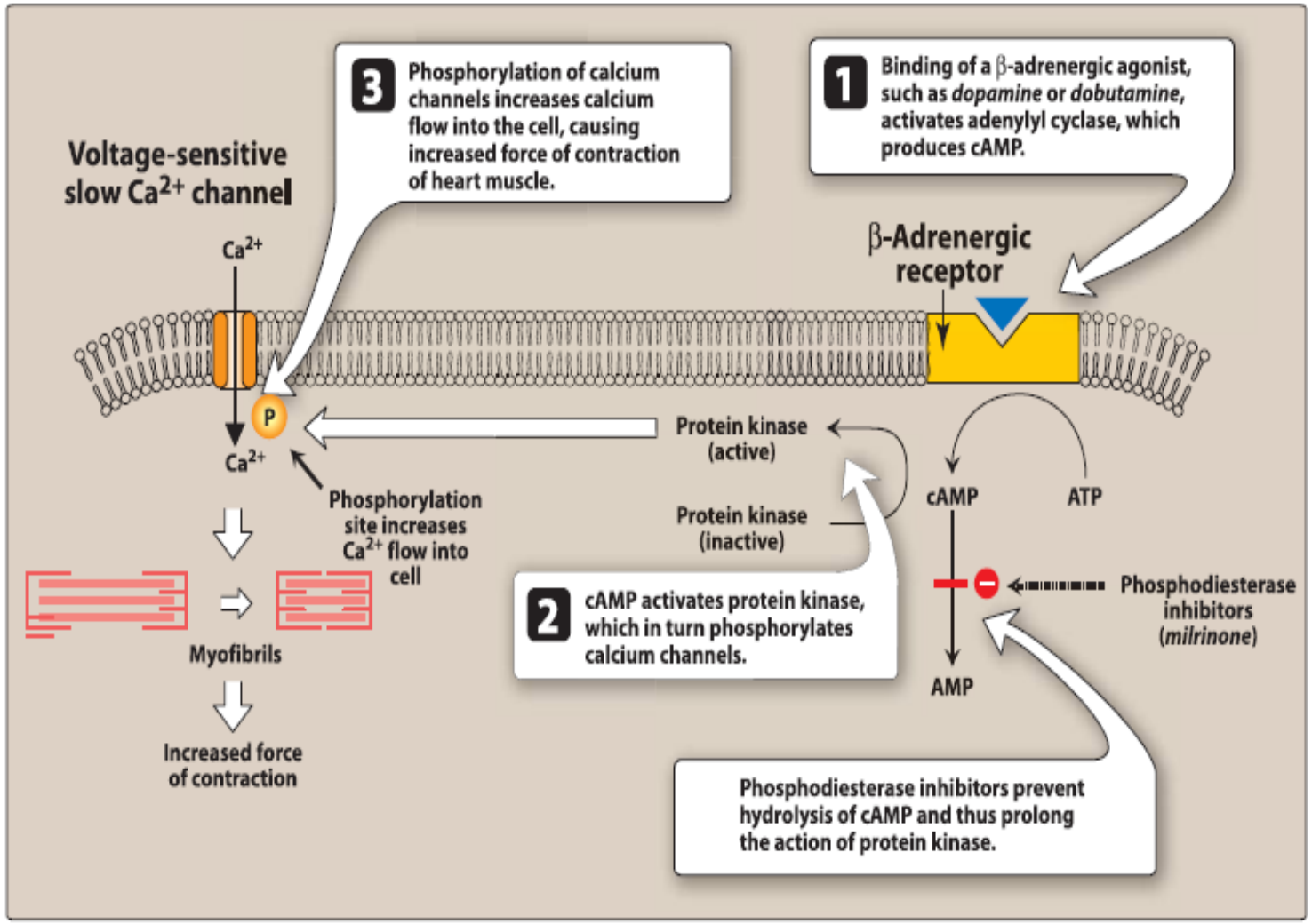
2. **Increased contractility of the cardiac muscle**: Digoxin increases the force of cardiac contraction, causing cardiac output to more closely resemble that of the normal heart. Vagal tone is also enhanced, so both heart rate and myocardial oxygen demand decrease. Digoxin slows conduction velocity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

- **PK**: narrowing therapeutic index !!!
- **Adverse effects**: low dose ?? Anorexia, nausea, vomiting, blurred vision, or yellowish vision. High dose?? Arrhythmias!! , hypokalemia predispose digoxin toxicity, caution with P-gp inhibitors and drugs that slow AV conduction.


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).
Cardiac output
Normal
HF treated with digoxin
Untreated HF
A
B
C
D
E
Symptoms of inadequate output, such as fatigue
Ventricular end-diastolic pressure
Symptoms of excessive venous pressure
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.

11- Inotropic Drugs: B- β-Adrenergic agonists

- Dobutamine and Dopamine, improve cardiac performance by causing positive inotropic effects and vasodilation.
- **MOA**: increase entry of calcium ions into myocardial cells and enhanced contraction.
- **PK**: IV infusion and are primarily used in the short-term treatment of acute HF in the hospital setting.



11- Inotropic Drugs: C- Phosphodiesterase inhibitors

- **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.
- **PK**: IV infusion for short-term treatment of acute HF. However, *dobutamine* and *milrinone* may also be considered for intermediate-term treatment in the outpatient setting for palliative care !!

12- Recombinant B-type Natriuretic Peptide (rhBNP)

- **Nesiritide**: used when IV diuretics are minimally effective for acutely decompensated congestive heart failure.
- **MOA**: binding to natriuretic peptide receptors and stimulates natriuresis and diuresis and reduces preload and afterload.
- **PK**: IV (bolus or infusion?) t1/2? Clearance?
- **Adverse effects**: Hypotension and dizziness, and like diuretics, nesiritide can worsen renal function.

Order of Therapy