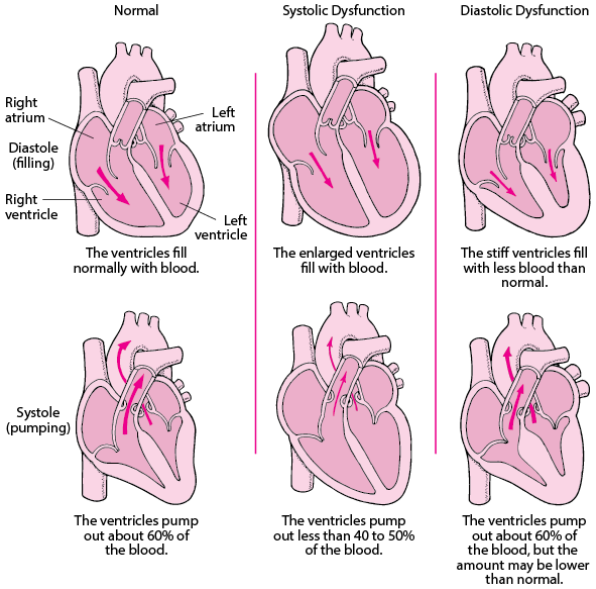
HEART FAILURE

I. Definitions

A. Heart Failure (HF)

- HF results when one or both ventricles are unable to pump sufficient blood to meet the body's needs.
- There are two types of heart failure:

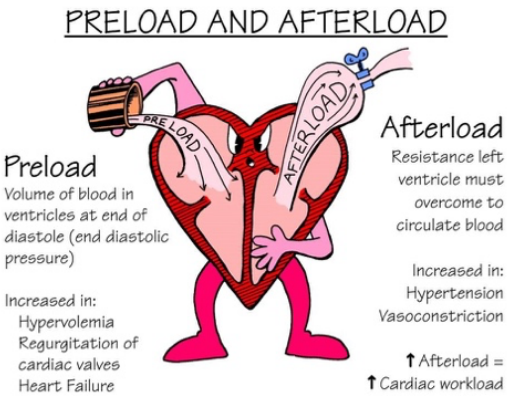
(1) HF*r*EF = heart failure with "reduced" ejection fraction (EF < 40%)
= "systolic" heart failure
- contractility is impaired
- enlarged ventricles fills with blood, but the ventricles pump out less than 40-50% of the blood → decreased cardiac output (CO)



(2) HF*p*EF = heart failure with "preserved" ejection fraction (EF = 50-75%)
= "diastolic" heart failure
- contractility is not impaired
- wall stiffness and thickness of ventricles prevents full relaxation and filling of the ventricle chamber
- normal EF, but SV & CO are low because end diastolic volume is low

B. Preload

- forces acting on the venous circulation that stretch myocardial fibers of the ventricles at the end of diastole = ventricular end-diastolic pressure (LVEDP)
- venous constriction increases blood volume entering the heart → increases ventricular stretch at end of diastole →increases end diastolic pressure → increases preload



C. Afterload

- forces acting on the arterial circulation that produce resistance which the left ventricle must overcome to pump blood out the aorta
- analogous to arterial resistance or pressure

D. Contractility

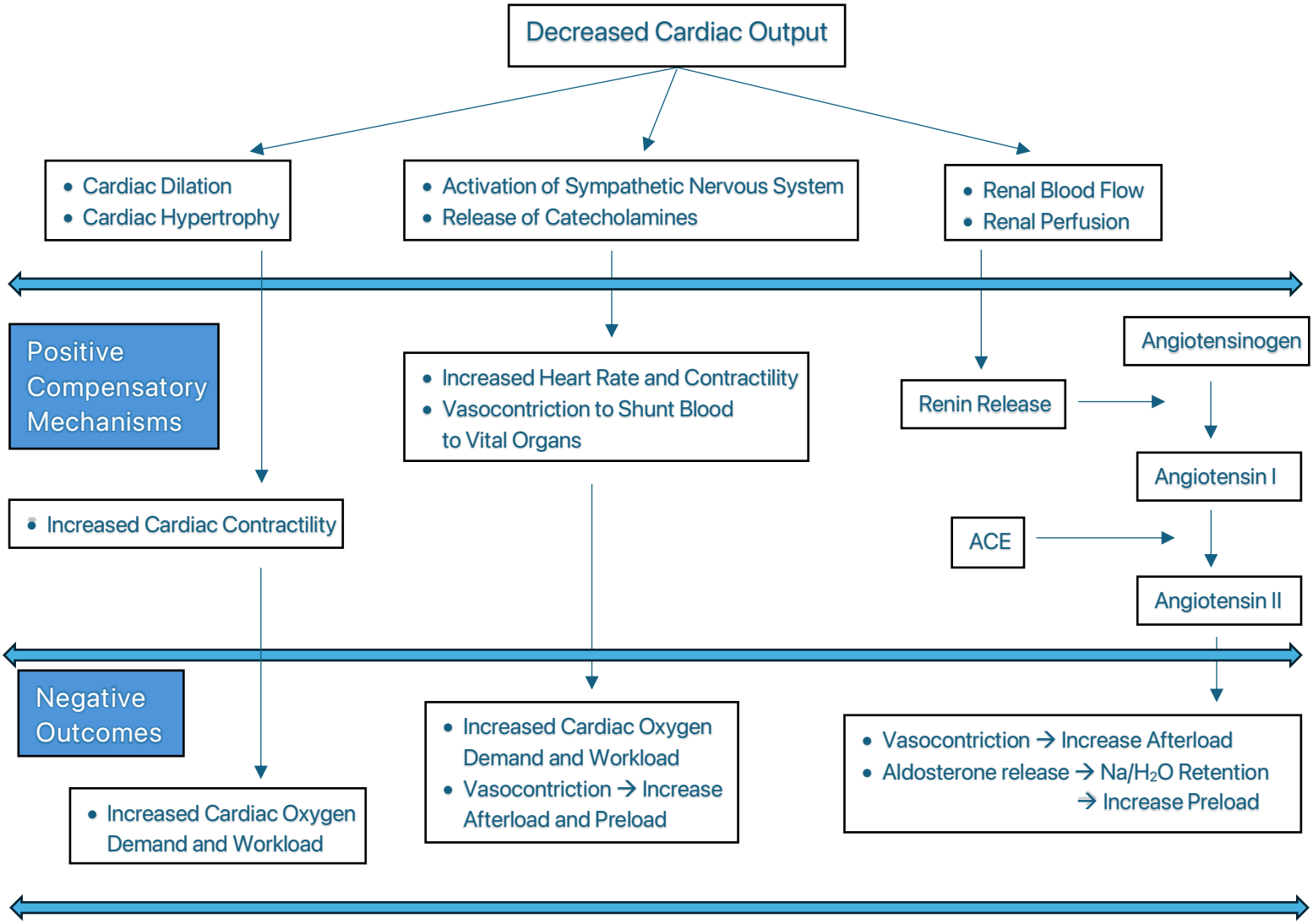
- the inherent ability of the myocardium to contract, independent of preload or afterload
- contractility is synonymous with inotropism

II. Signs and Symptoms of Heart Failure

- The symptoms of heart failure are traditionally divided into those that reflect left ventricular failure and/or right ventricular failure.

	Left Ventricular Failure	Right Ventricular Failure
Subjective	SOB (shortness of breath) DOE (dyspnea on exertion) Orthopnea (2-3 pillows) PND (paroxysmal nocturnal dyspnea) Weakness, Fatigue	Peripheral Edema Weakness, Fatigue
Objective	LVH (left ventricular hypertrophy) EF (ejection fraction) < 40% Reflex Tachycardia Increased BUN/Cr (d/t poor renal perfusion)	Weight Gain (fluid retention) Jugular Vein Distension Hepatomegaly / Ascites

III. Adaptive Mechanisms in Heart Failure



IV. Non-Pharmacologic Inventions

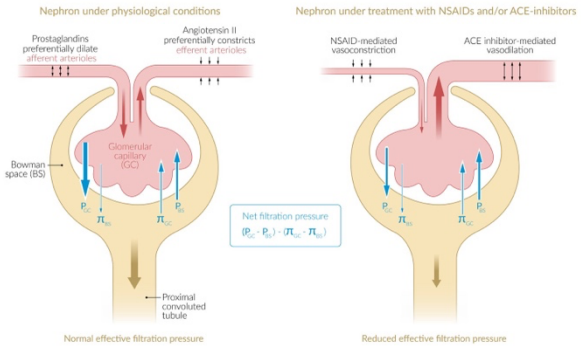
A. Elimination of Drugs that may Induce Heart Failure

(1) Negative Inotropic Agents

- Non-Dihydropyridine Calcium Channel Blockers: Diltiazem and Verapamil
- Beta-Blockers during Acute Decompensated Heart Failure

(2) Expansion of Plasma Volume

- NSAIDs → renal prostaglandin inhibition
  → Na/H_2O retention
- Glucocorticoids (e.g., prednisone)
  → renal prostaglandin inhibition
  → Na/H_2O Retention
- Direct-Acting Vasodilators: Hydralazine and Minoxidil →Activation of RAAS System
  → Aldosterone Release
  → Na/H_2O Retention



B. Low Sodium Diet (< 2 Grams/Day)

C. Bedrest During Acute Episodes of HF

D. Light Exercise when Patient is Stable

V. Pharmacologic Interventions

A. Diastolic Heart Failure (HFpEF)

- Treatment of DHF remains empiric since trial data are limited.
- General principles in treatment of DHF include:
  (1) control systolic and diastolic hypertension
  (2) control heart rate, particularly in atrial fibrillation
  (3) control peripheral and pulmonary edema with diuretics
  (4) digoxin is generally not used in DHF since systolic function is intact.

B. Systolic Heart Failure (HFrEF)

- The following drug classes are associated with improved survival benefit in systolic HF:
  - RAS blockers (ACE-I, ARB), ARNI (angiotensin receptor/naprilysin inhibitor), and beta blockers (BB) are considered 1st-line agents in systolic HF → documented to improve survival and improved quality of life in systolic HF.
    - beta blockers have a compelling 1st line agents in patients with HF and atrial fibrillation and/or angina pectoris.
  - MRA (mineralcorticoid receptor antagonists = aldosterone antagonists): spironolactone and eplerenone may be added to a RAS blocker, ARNI, and BB regimen while closely monitoring serum K levels.
  - SGLT-2 inhibitors: Dapagliflozin (Farxiga) and Empagliflozin (Jardiance) have recently demonstrated reduced mortality and rehospitalizations in patients with HFrEF.

Systolic Heart Failure (continued)

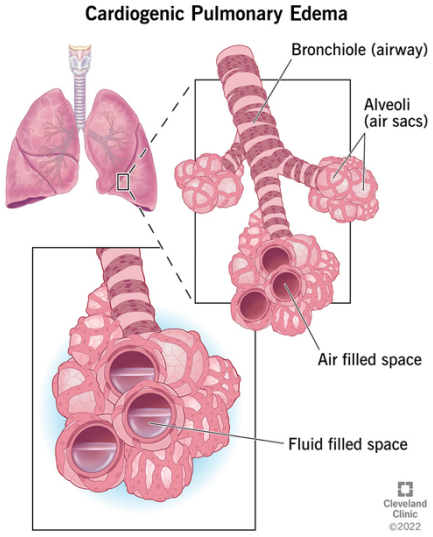
- The following drug classes have not demonstrated improved survival benefit in HFrEF.
    - Diuretics are mainstay agents in HF, since they serve an essential role in maintaining optimal fluid balance and treating peripheral and pulmonary edema.
    - Digoxin is a positive inotropic agent primarily used in HF patients with atrial fibrillation or HF patients with chronically low blood pressure.

- **Summary of Primary Agents Used in Systolic Heart Failure** (UpToDate 2024)

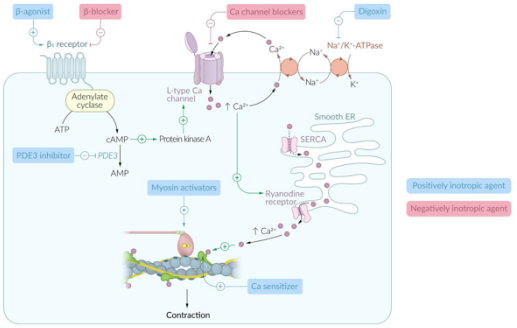
Type of therapy	Role in therapy	Drug	Typical initial dose (oral)	Target dose
Renin-angiotensin system inhibitors/neprilysin inhibitors	Preferred	Sacubitril-valsartan (ARNI)	24/26 to 49/51 mg twice daily*	97/103 mg twice daily
	Alternatives	Lisinopril	2.5 to 5 mg once daily	20 to 40 mg once daily
		Ramipril	1.25 to 2.5 mg once daily	10 mg once daily
		Enalapril	2.5 mg twice daily	10 to 20 mg twice daily
		Captopril	6.25 mg three times daily	50 mg three times daily
		Trandolapril	1 mg once daily	4 mg once daily
		Losartan	25 to 50 mg once daily	150 mg once daily
		Candesartan	4 to 8 mg once daily	32 mg once daily
		Valsartan	20 to 40 mg twice daily	160 mg twice daily
Beta blockers	Preferred	Carvedilol	3.125 mg twice daily	≤85 kg: 25 mg twice daily
				>85 kg: 50 mg twice daily
		Carvedilol CR	10 mg once daily	80 mg once daily
		Metoprolol succinate CR	12.5 to 25 mg once daily	200 mg once daily
		Bisoprolol	1.25 mg once daily$^{\Delta}$	10 mg once daily
Mineralocorticoid receptor antagonists	Preferred	Spironolactone	12.5 to 25 mg once daily	25 to 50 mg once daily or in two divided doses
		Eplerenone	25 mg once daily	50 mg once daily
SGLT2 inhibitors	Preferred	Dapagliflozin	10 mg once daily	
		Empagliflozin	10 mg once daily	
	Alternative	Canagliflozin	100 mg once daily	

- **Diuretics**

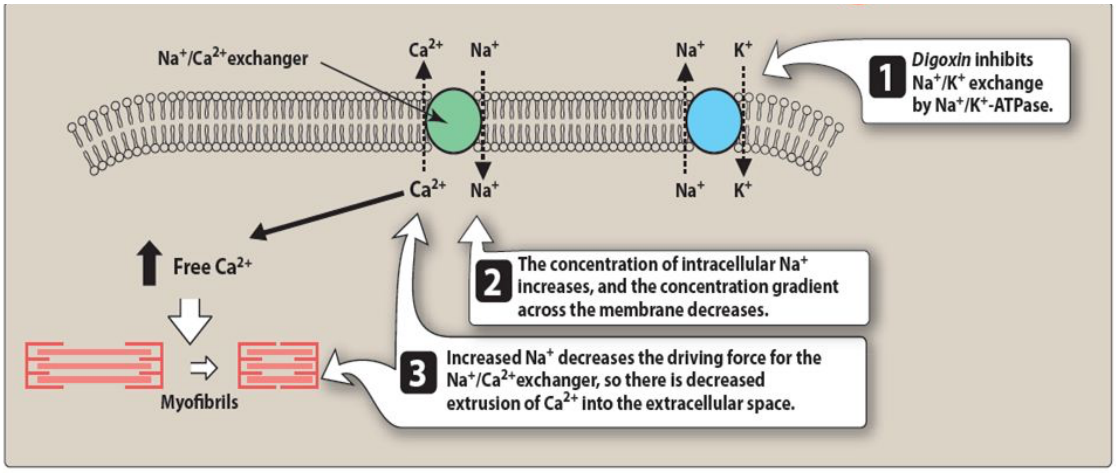
    - Diuretics are indicated when sodium restriction fails to control volume expansion in HF.
    - The goal is to provide symptomatic relief of HF when treating peripheral and pulmonary edema, without causing intravascular depletion.
    - In patients with renal insufficiency (i.e., CrCl < 30 ml/min), the Loop diuretics are indicated for an effective diuretic response.
    - KCl supplements may be required to prevent hypokalemia (serum K < 3.5)



- **Digoxin (Lanoxin)**
  - Mechanism of Action
    - Digoxin improves cardiac output (CO) by increasing myocardial force of contraction in patients with systolic heart failure.
    - Digoxin is considered a 2nd-line treatment in systolic heart failure, used primarily in patients with a concomitant supraventricular arrhythmia (SVT, atrial fibrillation) or in patients with chronically low blood pressure.

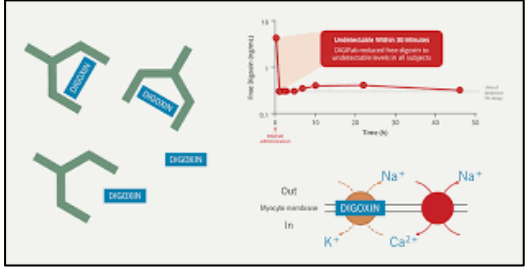


    - Digoxin is not used in diastolic heart failure (HFpEF), since systolic function is intact.

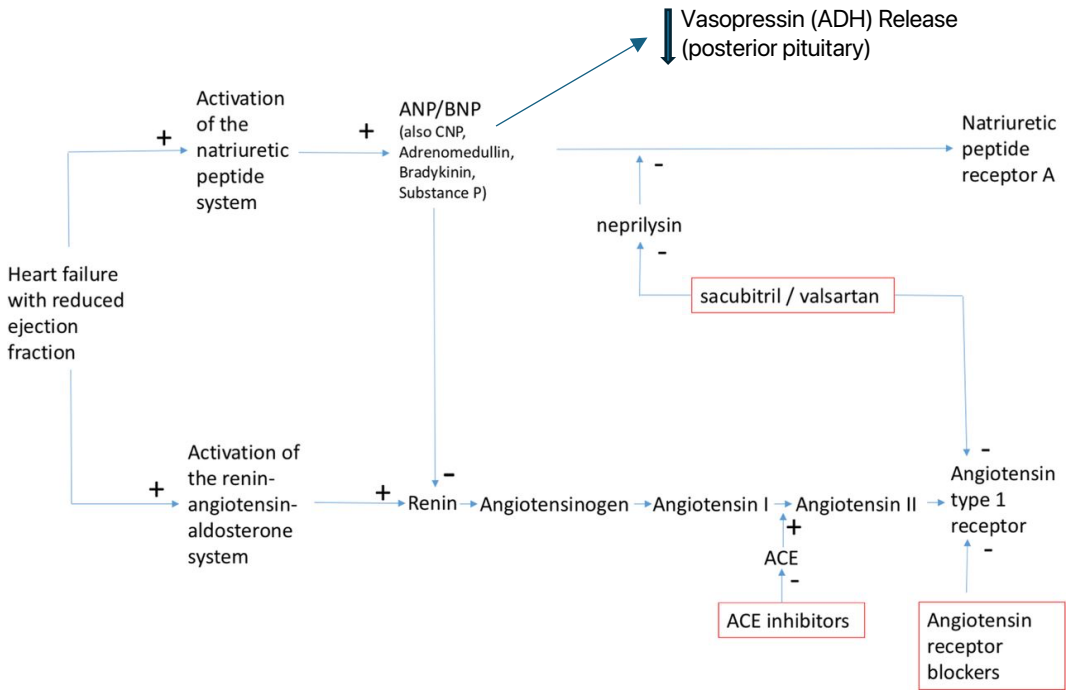


  - Digoxin Adverse Effects → most prevalent when serum digoxin levels are > 2 mcg/L or when serum K < 3.0 mEq/L (normal: 3.5-5.2 mEq/L).
    - Cardiac: bradycardia (HR < 50) due to AV block
    - GI: anorexia, nausea/vomiting
    - Visual disturbances: altered color perception, haloes
    - Fatigue/Weakness
    - Hyperkalemia
    - Gynecomastia
  - Digoxin Therapeutic Serum Level: 0.5 – 2.0 mcg/L
    - Heart failure: 0.5 – 0.9 mcg/L
    - Atrial fibrillation: 0.5 -2.0 mcg/L
  - Digoxin Toxicity (Serum Digoxin > 2.4)
    - Digoxin immune fab (Digibind) is an antidote for digoxin toxicity → digoxin-specific antibody which binds to and inactivates digoxin

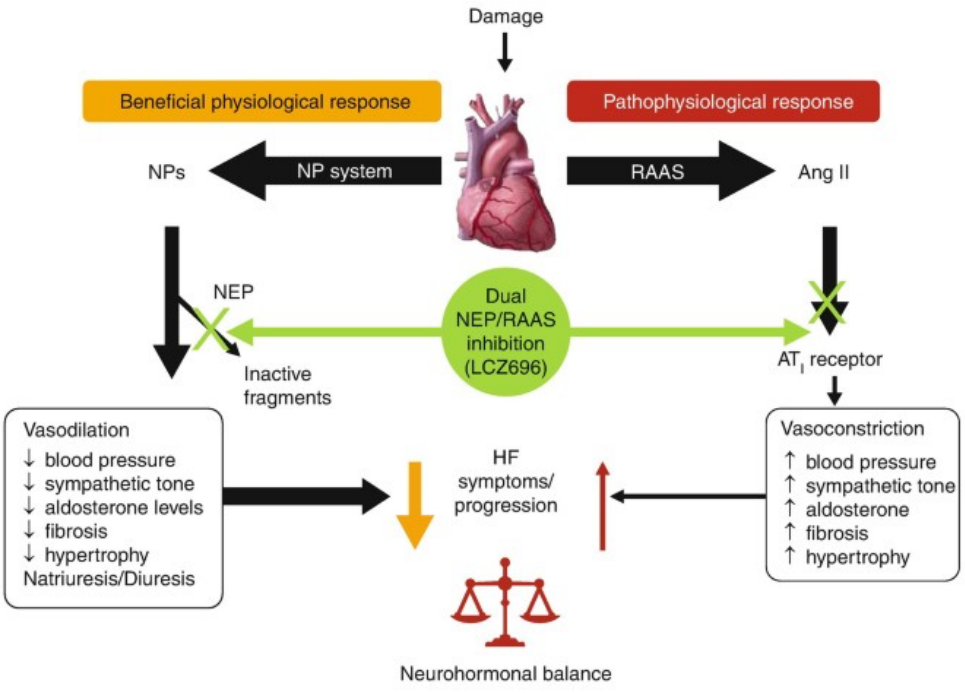
Digoxin Immune Fab (Digibind)



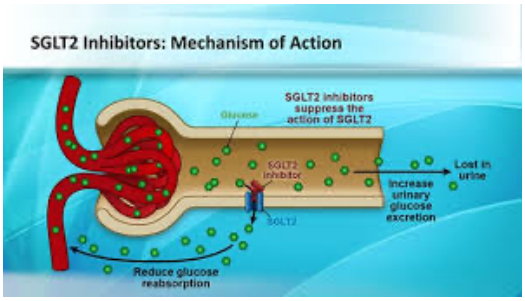
- **Entresto (Sacubitril / Valsartan)**
  - Entresto is an ARNI (angiotensin receptor / neprilysin inhibitor) used to replace an ACE-I or ARB in HFrEF.
    - Entresto in a large clinical trial (Paradigm-HF) proved to be more effective than enalapril in reducing hospitalizations and mortality in patients with HFrEF.
  - Rx cost: Entresto ($736.00/month) vs Enalapril ($12.13/month)
  - Mechanism of Action: sacubitril inhibits neprilysin → increases ANP (atrial natriuretic peptide) and BNP (B-type natriuretic peptide) → inhibits RAAS and vasopressin release.



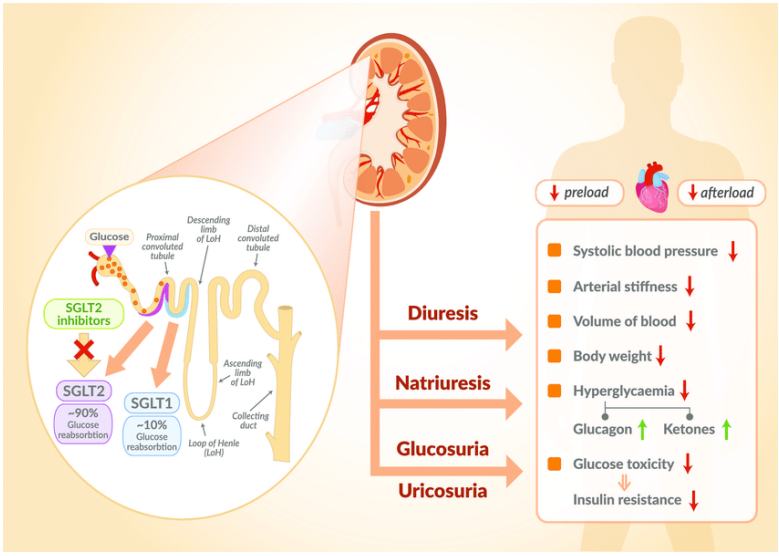
  - "Beneficial Physiological Response of NP System" vs "Pathophysiological Response of RAAS"



- **<u>SGLT-2 (Sodium-Glucose Cotransporter-2) Inhibitors</u>**: Dapagliflozin (Farxiga) and Empagliflozin (Jardiance)



  - <u>Mechanism of Action</u>: SGLT-2 inhibitors block Na+ and glucose reabsorption in proximal tubule of nephron → promote diuresis, natriuresis, glucosuria, and uricosuria
  - <u>Benefits in SGLT-2 Inhibitors in HFrEF</u>
    (1) <u>Diuresis and Natriuresis</u>
    → decrease blood volume
    → decrease in systolic BP
    → decrease in arterial wall stiffness
    (2) <u>Glucosuria and Uricosuria</u>
    → decrease in hyperglycemia
    → weight loss
    (3) <u>Preload and Afterload Reduction</u> → reduction in MACE (major adverse cardiovascular events) and hospitalization in HFrEF and Type II DM.



  - <u>Adverse Effects</u>: genital fungal infections (5 timers more common in females), UTI's, hypotension (due to volume depletion, esp. in patients taking other diuretics) → AKI, DKA (therefore, contraindicated in Type I DM), Fournier's gangrene (i.e., necrotizing fasciitis of the perineum).

C. Preload & Afterload Reducing Agents

<u>Predominantly Afterload Reduction (Arterial Dilators)</u>

(1) Direct-Acting Vasodilators
- Hydralazine (Apresoline)
- Minoxidil (Loniten)

(2) Channel Blockers (Dihydropyridine CCB)
- Amlodipine (Norvasc)
- Nifedipine (Procardia XL)

<u>Predominantly Preload Reduction (Venous Dilators)</u>

(1) Nitrates
- IV NTG: 5 mcg/min – titrate to effect
- Transdermal NTG: 5-40 mg/day (remove at bedtime)

<u>Mixed Afterload and Preload Reduction</u>

(1) ACE-Inhibitors
- Captopril (Capoten)
- Enalapril (Vasotec)
- Lisinopril (Prinivil, Zestril)

(2) ARB (Angiotensin Receptor Blockers)
- Valsartan (Diovan)
- Losartan (Cozaar)

(3) SGLT-2 Inhibitors
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

(4) ARNI (Angiotensin Receptor/Naprilysin Inhibitor)
- Secubitril / Valsartan (Entresto)