

Management & Treatment of Heart Failure

I. Definitions

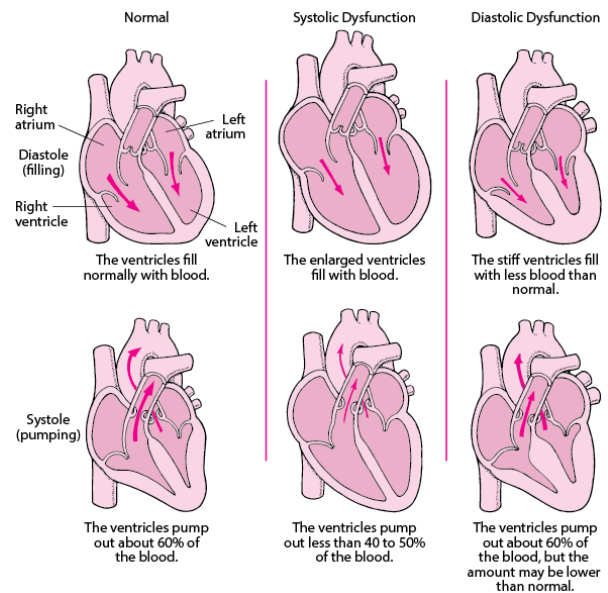
A. Heart Failure (HF)

- Heart failure (ACC/AHA) is a clinical syndrome with signs and symptoms caused by a structural and/or functional cardiac abnormalities, resulting in intracardiac pressures and/or reduced cardiac output.
 - Signs: edema, rales, jugular vein distention
 - Symptoms: fatigue, exercise intolerance, dyspnea (due to pulmonary congestion)
 - Structural Abnormalities: LV dilation, hypertrophy, valvular disease
 - Functional Abnormalities: systolic dysfunction (reduced cardiac output → reduced organ perfusion), and diastolic dysfunction (increased filling pressures)

B. Types of Heart Failure

- (1) **HFrEF**: heart failure with “reduced” ejection fraction = “systolic” heart failure

- $EF \leq 40\%$
- contractility is impaired
- enlarged ventricles fill with blood, but the ventricles pump out less than 40% of the blood → decreases cardiac output
- common causes: ischemic heart disease and long-standing hypertension (HTN)
- Treatment: 4 pillars (GDMT or Guideline-Directed Medical Therapy)
 - ACEi, ARB, or ARNI (angiotensin receptor neprilysin inhibitor)
 - Beta Blockers: carvedilol (Coreg), metoprolol succinate (Toprol XL), bisoprolol (Zybata)
 - Mineralocorticoid Receptor Antagonist = MRA: spironolactone, eplerenone
 - SGLT2i: dapagliflozin (Farxiga), empagliflozin (Jardiance)
- Additional Treatment: diuretics for congestion, hydralazine/isosorbide dinitrate (especially for Black patients), digoxin (especially in patients with atrial fibrillation)



- (2) **HFpEF**: heart failure with “preserved” ejection fraction = “diastolic” heart failure

- $EF \geq 50\%$
- contractility is not impaired
- wall stiffness and thickness of ventricles prevent full relaxation and filling of the ventricle chamber → elevated filling pressures
- normal EF, but SV & CO are low because end diastolic volume is low
- common causes: HTN, obesity, diabetes, atrial fibrillation (AF), aging, CKD.
- Treatment:
 - symptomatic management and risk factor control (BP, weight, DM, AF)
 - SGLT2i (Class I recommendation)
 - MRAs and ARNIs (Class IIb recommendation)
 - diuretics for volume overload

Types of Heart Failure (cont.)

(3) **HFmrEF**: heart failure with “mildly” reduced ejection fraction

- EF 41- 49%
- mixed features of systolic and diastolic dysfunction, i.e., transition zone between HFrEF and HFpEF
- treat like HFrEF: GDMT (BB, ACEi/ARB/ARNI, MRA, SGLT2i) → evidence-based treatment shown to reduce mortality and hospitalizations

(4) **HFimpEF**: heart failure with “improved” ejection fraction

- prior EF $\leq 40\%$, but now improved systolic function to $> 40\%$ with GDMT
- interpretation: recovery or partial reversal of HFrEF due to effective GDMT; however, the underlying pathophysiology persists and withdrawal of GDMT leads to relapse of HFrEF
- note: “improvement” in HFimpEF indicates remission, not a cure
- management: continue full GDMT

SUMMARY: HEART FAILURE CLASSIFICATION

Category	Definition (LVEF)	Pathophysiology	Typical Causes	Key Management Principles
HFrEF (Heart Failure with Reduced EF)	$\leq 40\%$	Systolic dysfunction — decreased contractility and impaired LV emptying	Ischemic heart disease, dilated cardiomyopathy, post-MI	4 Pillars of GDMT: 1 ARNI / ACEI / ARB 2 Evidence-based β-blocker 3 MRA 4 SGLT2 inhibitor + Diuretics
HFmrEF (Heart Failure with Mildly Reduced EF)	41–49%	Mixed features of systolic and diastolic dysfunction	Transition zone between HFrEF and HFpEF	Treat like HFrEF: Use GDMT as tolerated (SGLT2i, β -blocker, ACEi/ARB/ARNI, MRA) — shown to reduce hospitalizations and mortality
HFpEF (Heart Failure with Preserved EF)	$\geq 50\%$	Diastolic dysfunction — impaired relaxation and increased stiffness of LV; normal EF but elevated LV filling pressures	Long-standing hypertension, obesity, diabetes, CKD, AF, aging	Comorbidity-focused: Control BP, weight, AF, diabetes SGLT2 inhibitor (empagliflozin/dapagliflozin – Class I) Consider ARNI, MRA, diuretics for volume control
HFimpEF (Heart Failure with Improved EF)	Previously $\leq 40\%$, now $> 40\%$	Recovery of systolic function (usually from GDMT)	Prior HFrEF that responded to therapy	Continue full GDMT indefinitely — improvement represents <i>remission</i> , not cure; stopping therapy risks relapse

Concept Summary

- **HFrEF**: “Pump Failure” (weak contraction)
- **HFpEF**: “Filling Problem” (stiff ventricle)
- **HFmrEF**: “Gray Zone” (some systolic and some diastolic dysfunction)
- **HFimpEF**: “Recovered EF” (needs lifelong therapy maintenance with GDMT)

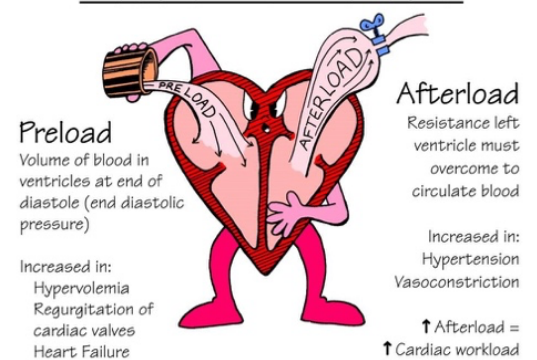
Summary: Guideline-Directed Medical Therapy

- HFrEF: ACEi, ARB, or ARNI; BB, MRA, SGLT2i.
- **SGLT2i’s** are the only class of drugs beneficial across all EF categories (Class 1A).
- **ARNI and MRA** have the strongest evidence in HFrEF, with emerging role in HFpEF.
- **HFimpEF** patients must stay on full HFrEF therapy (i.e., GDMT) to prevent relapse.
- **Manage comorbidities** (HTN, DM, AF, etc...).

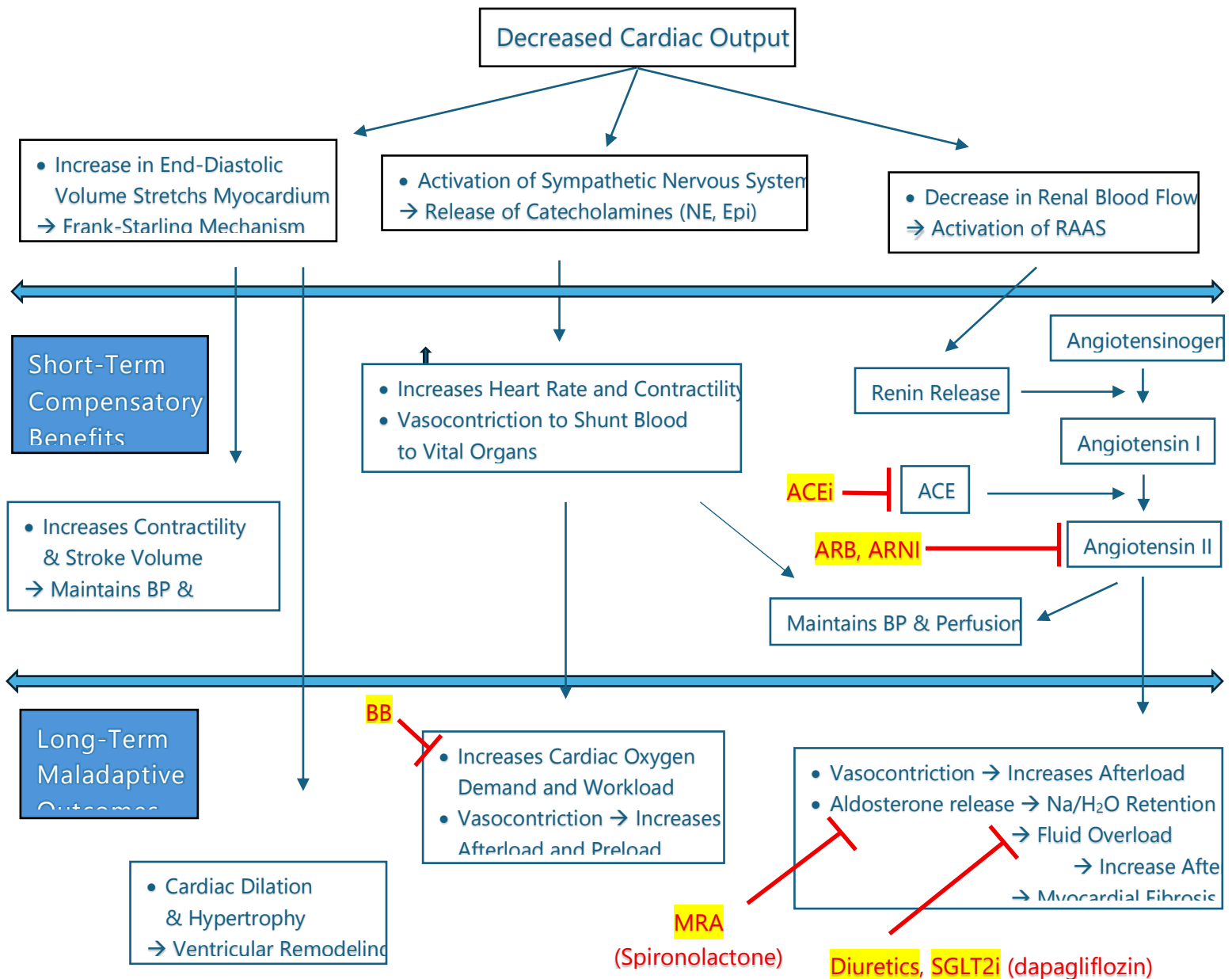
C. Preload, Afterload, and Contractility

- (1) 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
- (2) Afterload: forces acting on the arterial circulation that produce resistance which the left ventricle must overcome to pump blood out the aorta → arterial resistance/pressure
- (3) Contractility: the inherent ability of the myocardium to contract, independent of preload or afterload → synonymous with “inotropism”

PRELOAD AND AFTERLOAD



II. Adaptive Mechanisms in Heart Failure Due to Reduced Cardiac Output



III. Non-Pharmacologic Interventions

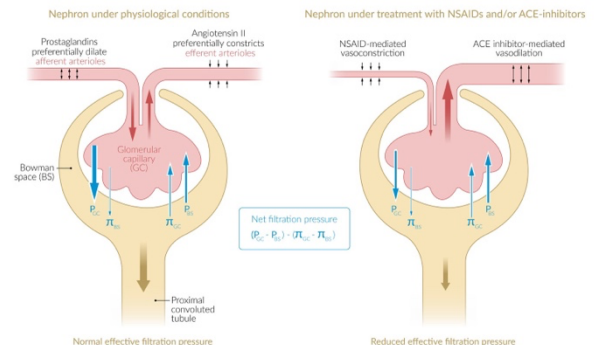
A. Elimination of Drugs that may Exacerbate Heart Failure

(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 → inhibit renal prostaglandin (PGI_2)
→ $\text{Na}^+/\text{H}_2\text{O}$ retention
- glucocorticoids (e.g., prednisone)
→ inhibit PGI_2
→ $\text{Na}^+/\text{H}_2\text{O}$ retention
- direct-acting vasodilators: hydralazine and minoxidil → activation of RAAS System
→ aldosterone release
→ $\text{Na}^+/\text{H}_2\text{O}$ retention



B. Low Sodium Diet (< 1500 mg/day, AHA)

C. Bedrest During Acute Episodes of HF

D. Light Exercise when Patient is Stable

IV. Pharmacologic Interventions

A. Systolic Heart Failure (HFrEF)

- The following drug classes are associated with improved survival benefit in HFrEF:
 - (1) RAS blockers (ACEi, ARB), ARNI (angiotensin receptor/neprilysin inhibitor) are considered 1st-line agents in HFrEF → documented to improve survival and improved quality of life in HFrEF.
 - (2) Beta Blockers: metoprolol succinate (Toprol XL), carvedilol (Coreg), bisoprolol (Zebata)
 - Note: BBs are compelling 1st-line agents in patients with HF and atrial fibrillation and/or angina pectoris.
 - (3) MRA (mineralocorticoid receptor antagonists): spironolactone (Aldactone) and eplerenone (Inspra)
 - MRAs may be added to a RAS blocker, ARNI, and BB regimen while closely monitoring serum K levels.
 - (4) SGLT-2 inhibitors: Dapagliflozin (Farxiga) and Empagliflozin (Jardiance)
 - SGLT2i's have recently demonstrated reduced mortality and rehospitalizations in patients with HFrEF.

Systolic Heart Failure (HFrEF) 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 chronically low blood pressure.

Summary of Primary Agents Used in Systolic Heart Failure (UpToDate 2025)

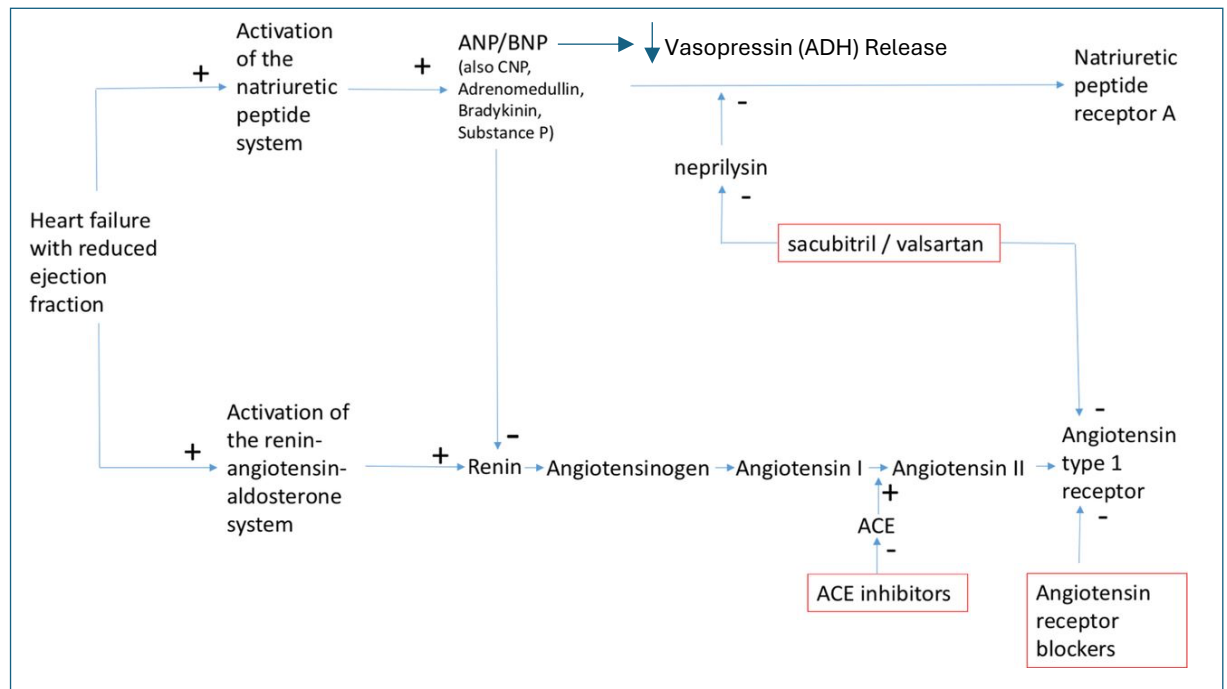
Type of therapy	Role in therapy	Drug	Typical initial dose (oral)	Target dose
Renin-angiotensin system inhibitors/neprilysin inhibitors	Preferred	Sacubitril-valsartan (ARNI)	24/26 to 49/51 mg twice daily*	97/103 mg twice daily
	Alternatives	Lisinopril	2.5 to 5 mg once daily	20 to 40 mg once daily
		Ramipril	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 ^Δ	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	

B. Diastolic Heart Failure (HFpEF)

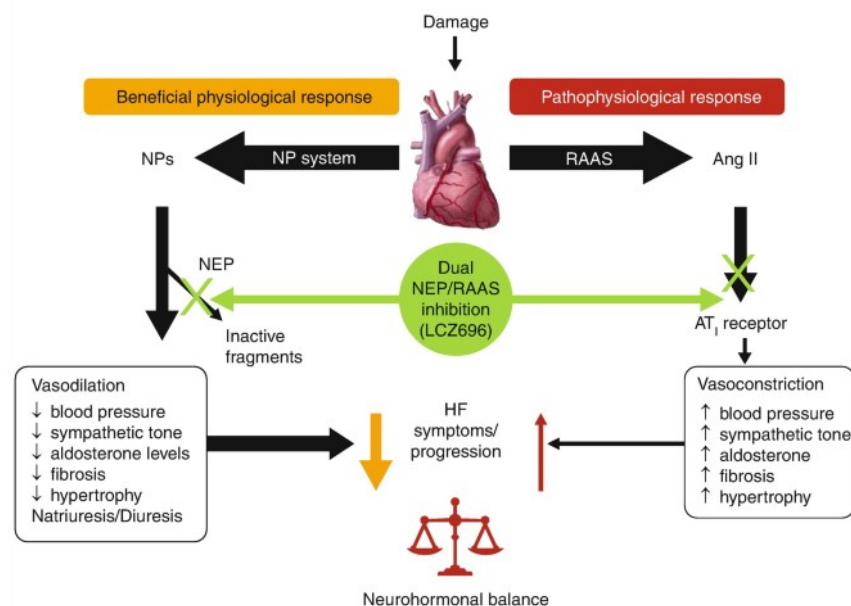
- Manage comorbidities: HTN, AF, DM, obesity
- SGLT2i's: empagliflozin (Jardiance) and dapagliflozin (Farxiga) have demonstrated survival benefit in HFpEF (Class IA recommendation).
- MRNAs: spironolactone (Aldactone) and eplerenone (Inspra) are Class IIb recommendations in HFpEF.
- ARNI: valsartan/sacubitril (Entresto) is also classified as a Class IIb recommendation in HFpEF.
- Diuretics are used for volume overload.
- Digoxin is generally not used in HFpEF, since systolic function is intact; however, it is primarily used in HFpEF patients with a concomitant SVT, atrial fibrillation, or in patients with chronically low blood pressure.

C. 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 mortality by 20% and in reducing hospitalization in patients with HFrEF.
- Rx cost: Entresto (brand: \$736.00/month – generic: \$80-\$200/month) versus Vasotec (enalapril) generic cost - \$12/month.
- Mechanism of Action: sacubitril inhibits neprilysin → increases ANP (atrial natriuretic peptide) and BNP (B-type natriuretic peptide) → inhibits RAAS and vasopressin release.



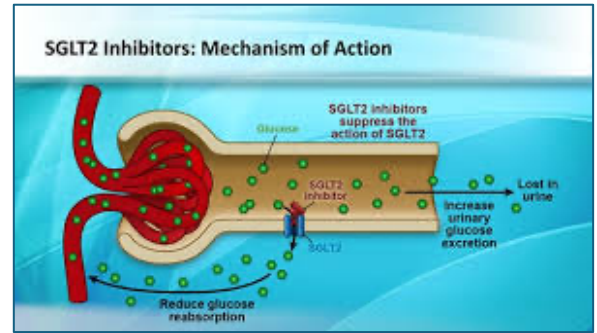
Beneficial Physiological Response of NP System versus Pathophysiological Response of RAAS



D. SGLT-2 (Sodium-Glucose Cotransporter-2)

Inhibitors: Dapagliflozin (Farxiga) and Empagliflozin (Jardiance)

- Mechanism of Action: SGLT-2 inhibitors block Na^+ and glucose reabsorption in proximal tubule of nephron → promote diuresis, natriuresis, glucosuria, and uricosuria.



- Benefits in SGLT-2 Inhibitors in HFrEF

(1) Diuresis and Natriuresis

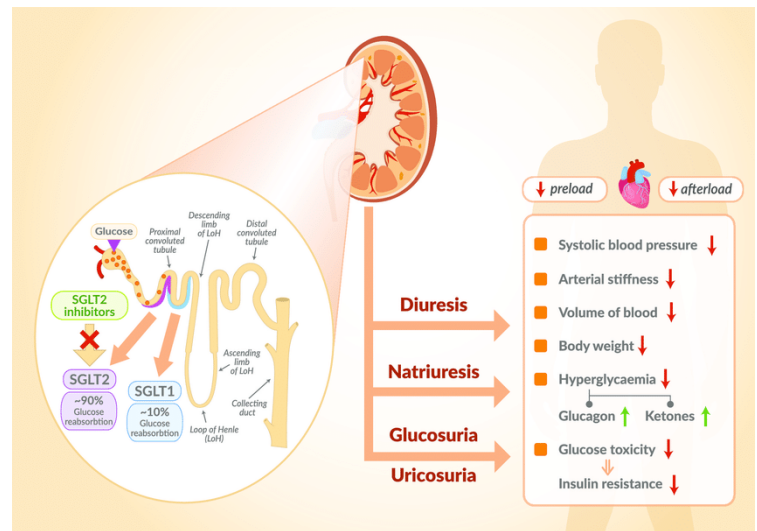
- decrease blood volume
- decrease in systolic BP
- decrease in arterial wall stiffness

(2) Glucosuria

- decrease hyperglycemia
- weight loss

(3) Preload and Afterload

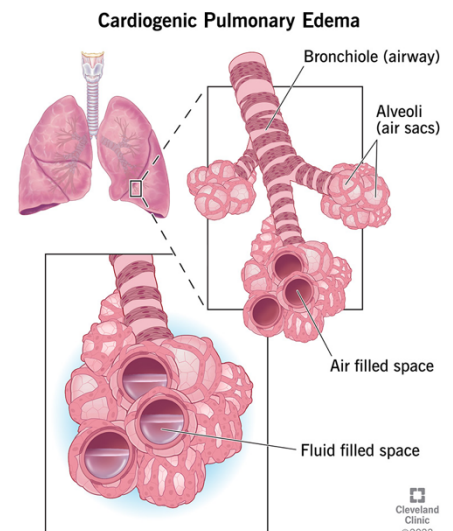
Reduction → reduction in MACE (major adverse cardiovascular events) and hospitalization in HFrEF and Type II DM.



- Adverse Effects: genital fungal infections (5 times 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).

E. Diuretics

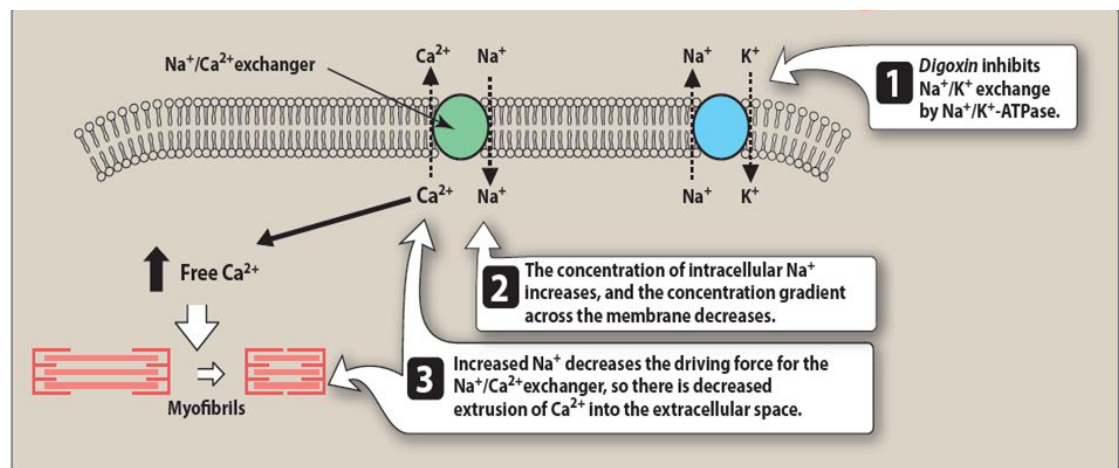
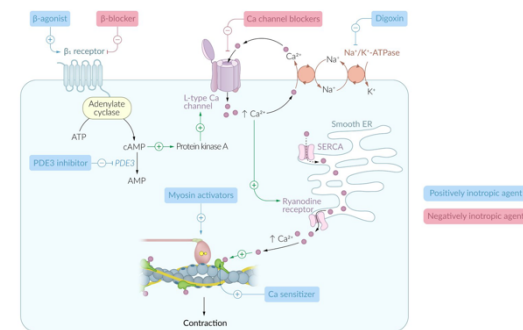
- diuretics are indicated when sodium restriction fails to control volume expansion in HF
- the goal is to provide symptomatic relief of HF when treating peripheral and pulmonary edema, without causing intravascular depletion
- in patients with renal insufficiency (i.e., $\text{CrCl} < 30 \text{ mL/min}$),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



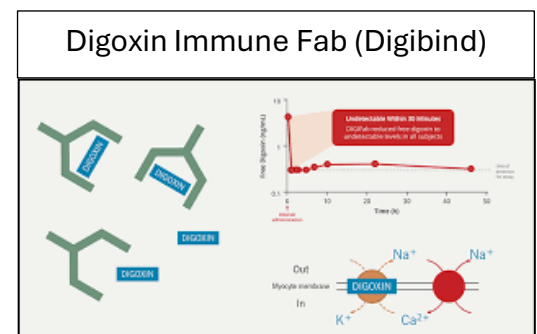
F. Digoxin (Lanoxin)

• Mechanism of Action

- digoxin improves cardiac output (CO) by increasing myocardial force of contraction in patients with systolic heart failure
- digoxin is considered a 3rd-line agent in HFrEF, used primarily in patients with a concomitant supraventricular arrhythmia (SVT), atrial fibrillation, or in patients with chronically low blood pressure



- Digoxin Adverse Effects are 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 bpm) 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



G. Preload & Afterload Reducing Agents

- **Predominantly Afterload Reduction (Arterial Dilators)**

Direct-Acting Vasodilators

- Hydralazine (Apresoline)
- Minoxidil (Loniten)

Channel Blockers (Dihydropyridine CCB)

- Amlodipine (Norvasc)
- Nifedipine (Procardia XL)

- **Predominantly Preload Reduction (Venous Dilators)**

Nitrates

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

- **Mixed Afterload and Preload Reduction**

ACE-Inhibitors

- Enalapril (Vasotec)
- Lisinopril (Prinivil, Zestril)

ARB (Angiotensin Receptor Blockers)

- Valsartan (Diovan)
- Losartan (Cozaar)

SGLT-2 Inhibitors

- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

ARNI (Angiotensin Receptor/Neprilysin Inhibitor)

- Sacubitril / Valsartan (Entresto)

H. Summary: Heart Failure Stages and Treatments (ACC/AHA Guidelines)

Stage	Description	Clinical Characteristics	Recommended Treatments
Stage A	At risk for HF but without structural heart disease or symptoms	- Hypertension - Diabetes - Coronary artery disease - Obesity - Metabolic syndrome - Family history of cardiomyopathy	- Lifestyle modification (diet, exercise, smoking cessation) - Control hypertension, diabetes, and lipid disorders - ACE inhibitors or ARBs if appropriate (e.g., diabetes or vascular disease) - Statins if indicated
Stage B	Structural heart disease but without signs or symptoms of HF	- Previous MI - Left ventricular remodeling (e.g., LV hypertrophy or low EF) - Asymptomatic valvular disease	- All Stage A recommendations - ACE inhibitors or ARBs (in all patients) - Beta-blockers (in all patients with reduced EF) - Consider implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) in select patients
Stage C	Structural heart disease with prior or current HF symptoms	- Known structural heart disease - Symptoms like fatigue, dyspnea, reduced exercise tolerance	- All Stage A and B recommendations - Diuretics for fluid retention - ACE inhibitors or ARBs or ARNIs - Beta-blockers - Aldosterone antagonists - SGLT2 inhibitors (e.g., dapagliflozin, empagliflozin) - Hydralazine/isosorbide dinitrate (especially in Black patients) - CRT, ICD in eligible patients - Lifestyle modifications - Patient education, care coordination
Stage D	Refractory HF requiring specialized interventions	- End-stage HF - Symptoms at rest despite optimal medical therapy - Frequent hospitalizations	- All treatments from Stage C - Advanced therapies: mechanical circulatory support (e.g., LVAD) - Heart transplant - Palliative care or hospice - Consider inotropes or experimental therapies - Frequent monitoring and multidisciplinary care