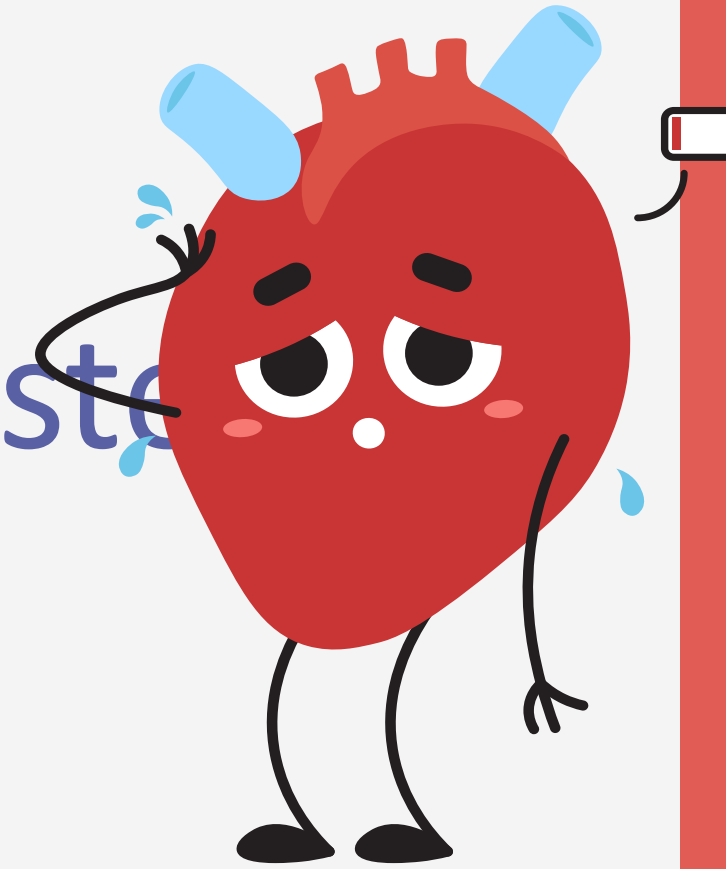
PHARMACOLOGY 201 | DR. MORA

Cardiovascular Syste



Heart failure medications

Learning Objectives

CHF Medications

1. Explain the pathophysiological changes in congestive heart failure (CHF) and how they inform the pharmacological targets for treatment.
2. Identify and classify the major drug classes used in CHF treatment, including diuretics, ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists, vasodilators, and inotropes.
3. Describe the mechanisms of action of commonly used CHF medications and how they contribute to symptom relief and improved cardiac function.
4. Discuss the concept of guideline-directed medical therapy (GDMT) in CHF and its impact on morbidity and mortality.
5. Explain the role of diuretics in CHF management, including indications, dosing strategies, and monitoring parameters.
6. Outline the role of ACE inhibitors, ARBs, and ARNI (angiotensin receptor-neprilysin inhibitors) in reducing afterload and improving cardiac output.

Learning Objectives

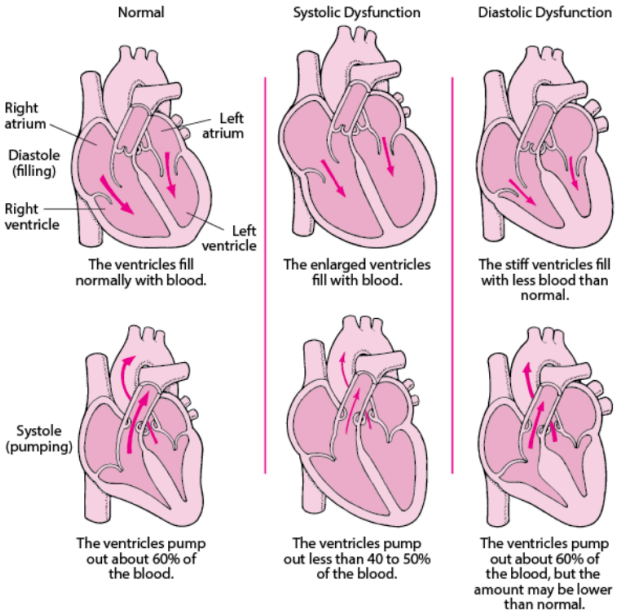
CHF Medications

7. Describe the benefits and clinical considerations of beta-blockers in CHF, including their use in heart failure with reduced ejection fraction (HFrEF).
8. Discuss the importance of aldosterone antagonists in CHF therapy and their role in preventing remodeling and electrolyte imbalances.
9. Explain the use of vasodilators, such as hydralazine and isosorbide dinitrate, in specific patient populations, including those with reduced renal function.
10. Evaluate the role of inotropic agents, such as digoxin and dobutamine, in the management of acute decompensated heart failure and end-stage CHF.

Heart Failure

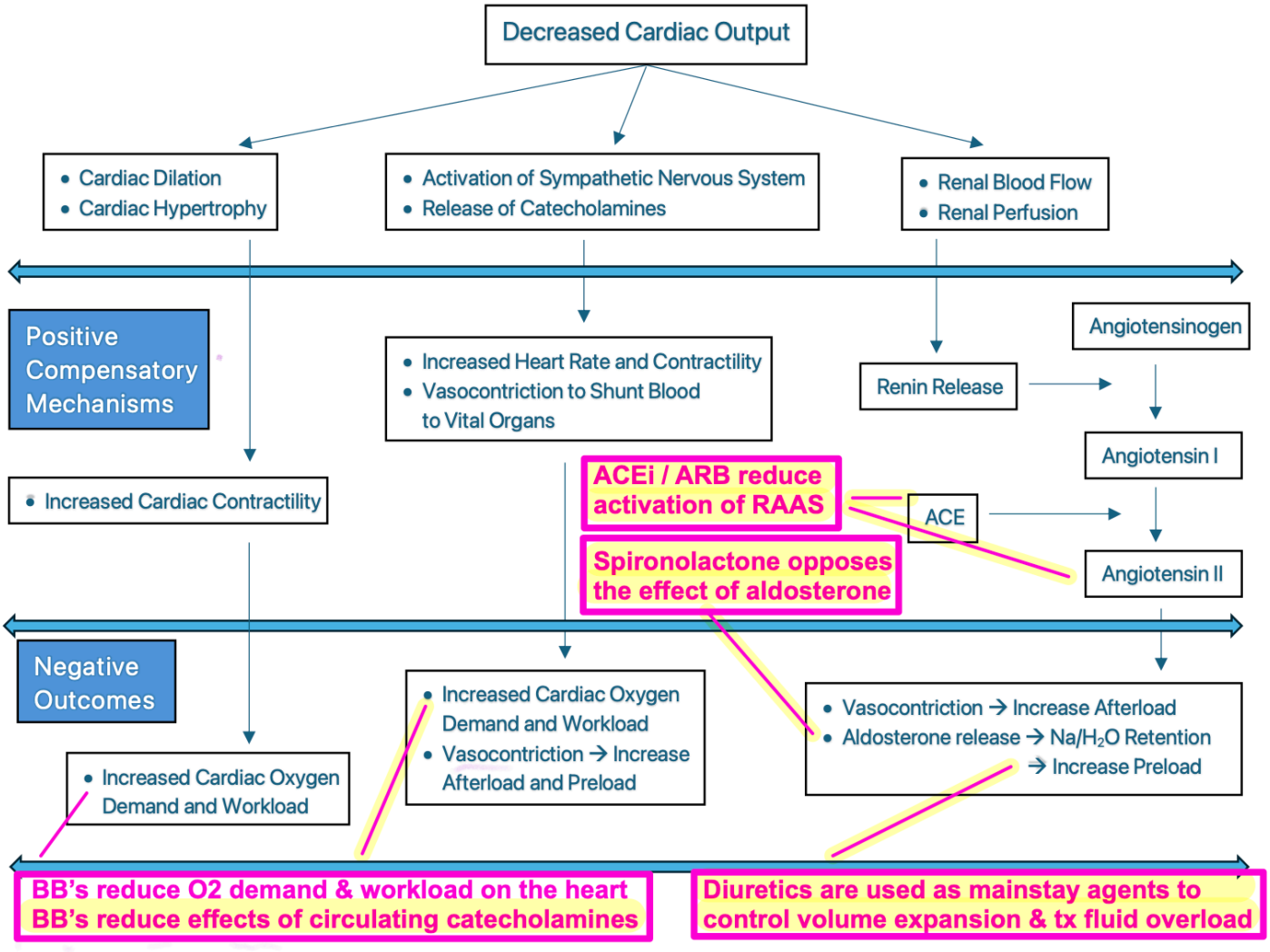
- There are two types of heart failure:

  (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)



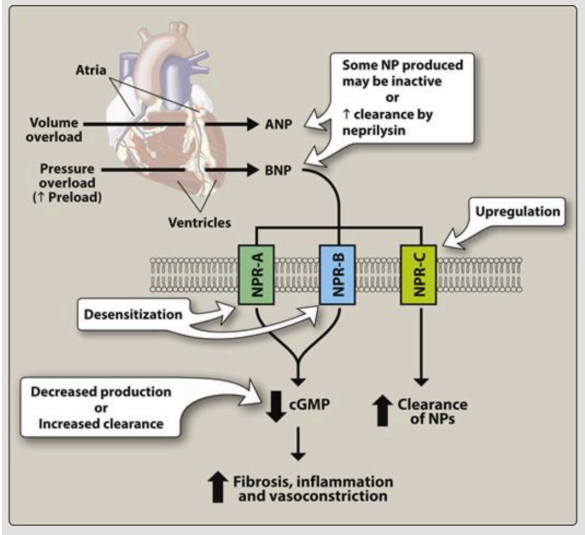
  (2) HF*p*EF = heart failure with "preserved" ejection fraction (EF = 50-75%)
  = "diastolic" heart failure
    - contractility is not impaired
    - wall stiffness and thickness of ventricles prevents full relaxation and filling of the ventricle chamber
    - normal EF, but SV & CO are low because end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

III. Adaptive Mechanisms in Heart Failure



Heart Failure: (1) chronic activation of the sympathetic nervous system and (2) chronic activation of RAAS, and (3) resistance to natriuretic peptides (NP: ANP, BNP), and (4) oxidative stress and inflammation —-> viscous cycle of remodeling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis —-> death.

- In HF, activation of the NPs (ANP, BNP) 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; however, NP receptors in HF become progressively desensitized or cGMP, a postreceptor messenger of NP, may be altered or decreased —> resistance to NP —> myocardial hypertrophy, fibrosis, inflammation, vasoconstriction, and reduced renal blood flow
- Neprilysin is the enzyme responsible for degradation of vasoactive peptides: A-I and A-II, bradykinin, and NPs (ANP, BNP). Inhibition of neprilysin augments the activity of the vasoactive peptides. To help offset activation of RAAS and bradykinin while maintaining benefits of natriuretic peptides, an ARB is combined with a neprilysin inhibitor. This inhibits RAAS activation but does not further potentiate bradykinin. All of this minimizes the risk of angioedema.



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

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

HCN CHANNEL BLOCKER
Ivabradine CORLANOR

INOTROPIC AGENTS
Digoxin LANOXIN
Dobutamine DOBUTREX
Dopamine GENERIC ONLY
Milrinone GENERIC ONLY

MINERALOCORTICOID RECEPTOR ANTAGONISTS
Eplerenone INSPRA
Spironolactone ALDACTONE

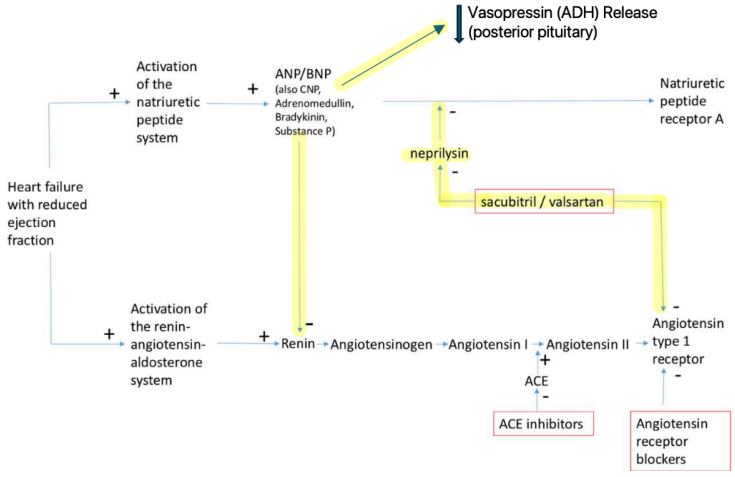
SGC STIMULATOR
Vericiguat VERQUVO

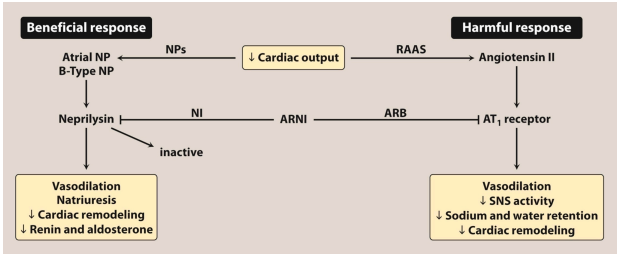
SGLT2 INHIBITORS
Dapagliflozin FARXIGA
Empagliflozin JARDIANCE

VASODILATORS
Hydralazine GENERIC ONLY
Isosorbide dinitrate DILATRATE-SR, ISORDIL
FDC Hydralazine/Isosorbide dinitrate BIDIL
Nitroglycerin GENERIC ONLY
Nitroprusside NIPRIDE, NITROPRESS

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.





Therapeutic Uses of Entresto

- Sacubitril/valsartan 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.
- The adverse-effect profile is similar to that of an ACE inhibitor or ARB. Because of the added reduction of afterload, hypotension is more common with an ARNI
- When switching from an ACEi, stop the ACE inhibitor for at least 36 hours prior to transitioning to an ARNI. This washout period is required to minimize the risk of angioedema

Beta Blockers

- The benefit of β-blockers is attributed, in part, to their ability to prevent the changes that occur because of chronic stimulation from the sympathetic nervous system. These agents decrease heart rate and inhibit release of renin from the kidneys. In addition, β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.
- Bisoprolol, carvedilol, and metoprolol succinate reduce morbidity and mortality associated with HFrEF.
- Bisoprolol and metoprolol succinate are selective beta-1 blockers (i.e. cardioselective) and carvedilol is a non-selective beta blocker.
- β-Blockers should also be used with caution with other drugs that slow atrioventricular (AV) conduction (negative dromotropy), such as amiodarone, verapamil, and diltiazem.

Diuretics

- Diuretics reduce signs and symptoms of volume overload, such as dyspnea on exertion, orthopnea, and peripheral edema.
- Diuretics decrease plasma volume —> decrease venous return to the heart (i.e., preload) —-> decreases cardiac workload and oxygen demand.
- Diuretics may also decrease afterload by reducing plasma volume, thereby further decreasing blood pressure.
- 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.
- Since diuretics have NOT been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess.

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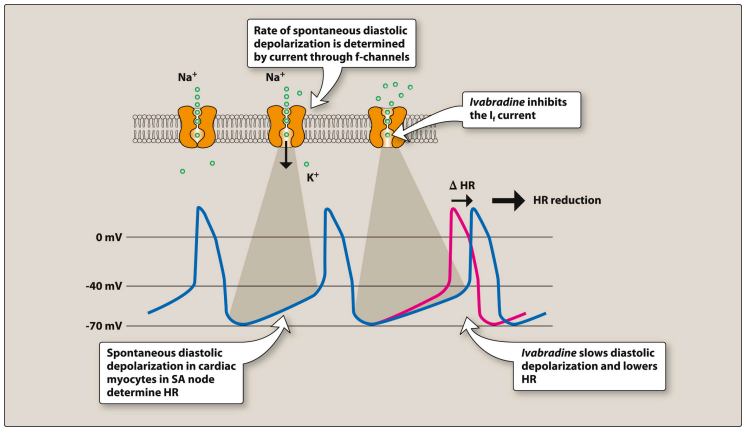
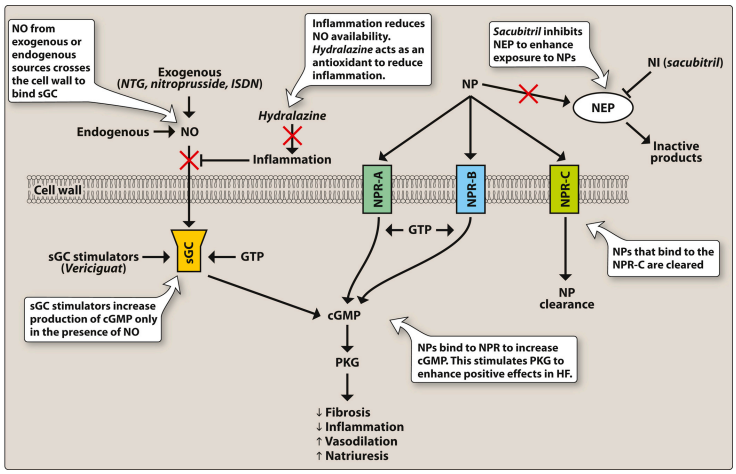
Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) Channel Blocker (HCN Channel Blocker): Ivabradine



- The 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 Reduction in heart rate (negative chronotropy) is use and dose dependent.
- 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.
- Therapeutic use: Ivabradine is utilized in HFrEF to improve symptoms in patients who are in sinus rhythm with a heart rate above 70 beats per minute and are on optimized HF pharmacotherapy.
- Patients should be on an optimal dose of β-blocker or have a contraindication to β-blockers.
- Side Effects: Bradycardia, which may improve with dose reduction of Ivabradine. Because ivabradine is mostly selective for the SA node, it is not effective for rate control in atrial fibrillation and has been shown to increase the risk of atrial fibrillation. Ivabradine inhibits similar channels in the eye, and luminous phenomena (for example, brightness or halos) may occur with therapy. This enhanced brightness may be ameliorated by dose reduction. Ivabradine should not be used in pregnancy or breast-feeding.

Arterial vasodilators: Hydralazine

- Hydralazine is an arterial vasodilator that may be used to reduce afterload and is most often used in combination with an oral nitrate in chronic HF.
- MOA: Hydralazine reduces calcium in arteriole smooth muscle leading to vasodilation —> reduces afterload —> increases 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.
- Therapeutic Use: If a 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 African-American patients with HFrEF on guideline-directed medical therapy (β-blocker plus ACE inhibitor or ARB).



ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide;
cGMP = cyclic guanosine monophosphate; CNP = C-type natriuretic peptide;
GTP = guanosine triphosphate; ISDN = isosorbide dinitrate; NEP = neprilysin;
NI = neprilysin inhibitor; NO = nitric oxide; NP = natriuretic peptide;
NPR = natriuretic peptide receptor; NTG = nitroglycerin; PKG = protein kinase G;
sGC = soluble guanylate cyclase.

- Side Effects: Headache, dizziness, hypotension, reflex tachycardia, and edema are common adverse effects. To mitigate the latter adverse effects, hydralazine should only be used if the patient is already on a β-blocker and a diuretic. Rarely, hydralazine has been associated with drug-induced lupus.

Nitrates: Isosorbide Dinitrate

- Nitrates contribute more to venodilation than arterial dilation.
- MOA: Nitrates quickly convert to NO and bind soluble guanylate cyclase (sGC). This activation increases intracellular cyclic guanosine monophosphate (cGMP) in smooth muscle cells. Cyclic GMP activates protein kinase G, which ultimately results in release of intracellular calcium, thereby producing vasodilation. Dilation of venous blood vessels leads to a decrease in preload by increasing venous capacitance, and dilation of arteries reduces systemic vascular resistance, reduces afterload, and increases cardiac output.
- Therapeutic Use: Isosorbide dinitrate is most often utilized in combination with hydralazine for self-identified African-Americans with HFrEF. Black patients most often have lower NO bioavailability and less RAAS activation, which makes this combination especially useful as compared with other ethnicities.
- Nitroglycerin and nitroprusside are utilized in IV form for the treatment of acute decompensated HFrEF in patients with signs of congestion and elevated systemic vascular resistance.
- Side Effects: Headache and dizziness can be dose limiting. The most common adverse effect of both intravenous nitroglycerin and nitroprusside is hypotension and its related signs and symptoms.

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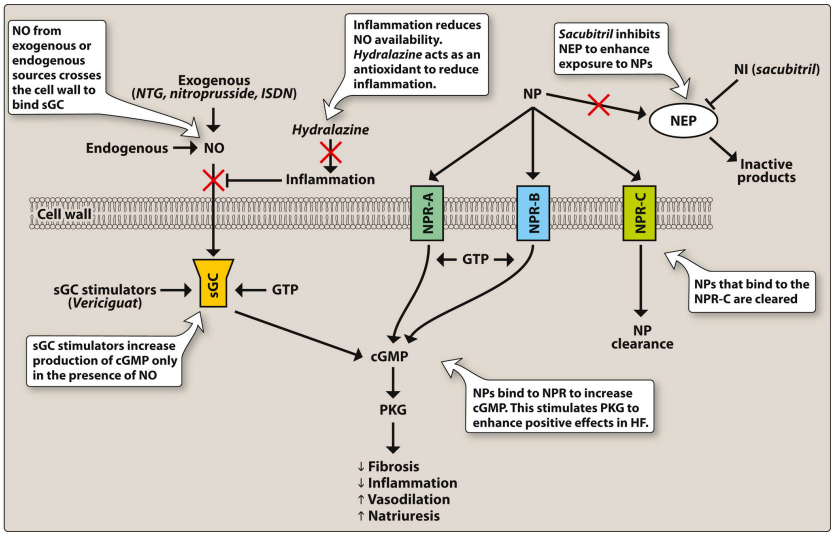
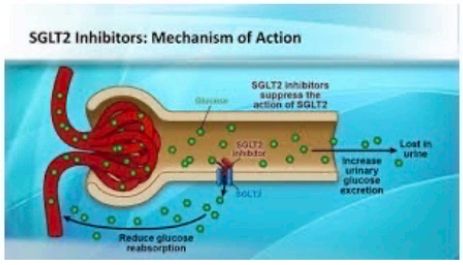
Soluble Guanylate Cyclase Stimulator (sGC Stimulator): Vericiguat

- Nitric oxide (NO) activates the enzyme-soluble guanylate cyclase (sGC) to stimulate production of cGMP. Oxidative stress and inflammation in HF inactivate endogenous NO and minimize the activation of sGC. This reduces the production of cGMP and contributes to vasoconstriction, fibrosis, and inflammation. sGC modulators increase sGC responsiveness to endogenous NO, thus correcting for the NO deficit in HF. This more physiologic approach to cGMP production limits hypotension, as compared with directly introducing exogenous NO.

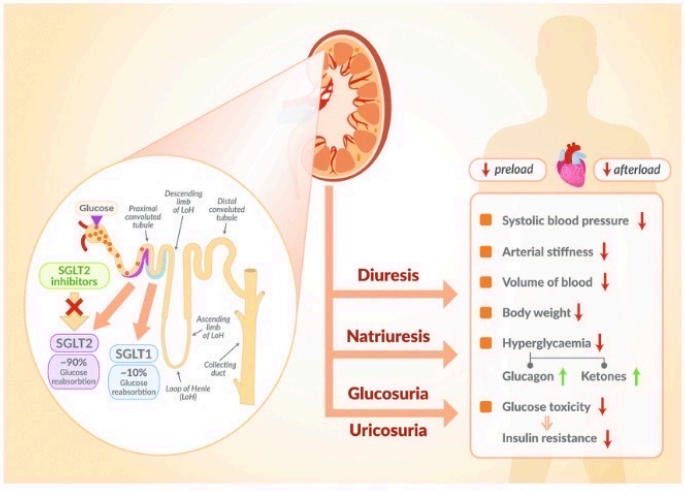


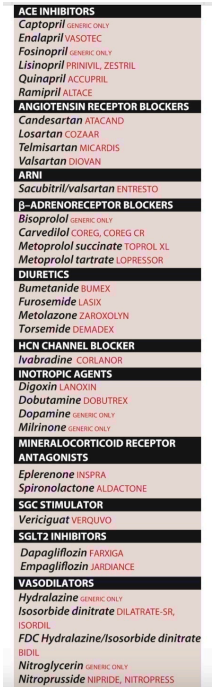
- MOA: Vericiguat directly stimulates sGC through a different binding site than NO and sensitizes sGC to endogenous NO. NO diffuses through cells to stimulate sGC to synthesize cGMP. An increase in cGMP activates protein kinase G to ultimately improve left ventricular compliance, vasodilate, reduce inflammation, and prevent hypertrophy and fibrosis. An sGC stimulator reduces the risk of HF hospitalization in those with evidence of recent acute decompensation.
- Therapeutic Use: An sGC stimulator may be started in patients with HFrEF who were recently hospitalized for HF and are on guideline-directed medical therapy.
- Vericiguat is orally administered.
- Side Effects: Hypotension, syncope, and anemia may occur. Vericiguat is contraindicated in pregnancy due to an increased risk of cardiac malformations and should not be used in breast-feeding. Use of vericiguat should be avoided with nitrates or phosphodiesterase inhibitors due to the risk of excessive hypotension.

›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 and Uricosuria
    - → decrease in hyperglycemia
    - → weight loss
  - (3) Preload and Afterload Reduction → reduction in MACE (major adverse cardiovascular events) and hospitalization in HFrEF and Type II DM.



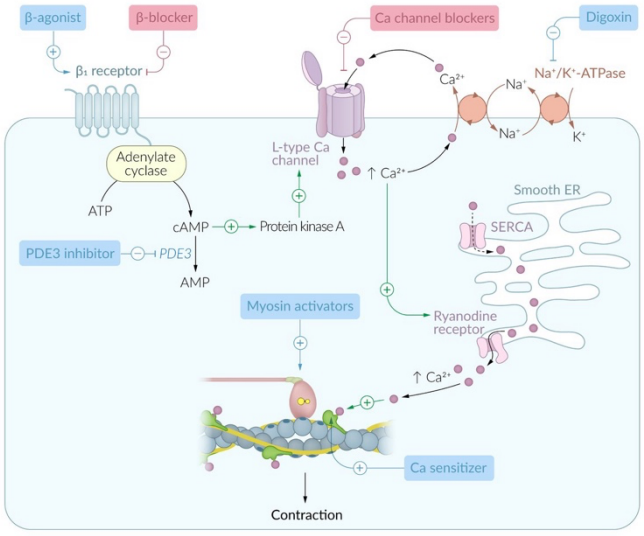


- Adverse Effects: genital fungal infections (5 timers more common in females), UTI's, hypotension (due to volume depletion, esp. in patients taking other diuretics) → AKI, DKA (therefore, contraindicated in Type I DM), Fournier's gangrene (i.e., necrotizing fasciitis of the perineum).

- Therapeutic Use: SGLT2 inhibitors should be considered in patients with symptomatic HFrEF who are on optimal HF pharmacotherapy with β-blockers, ACE inhibitors, and MRAs.

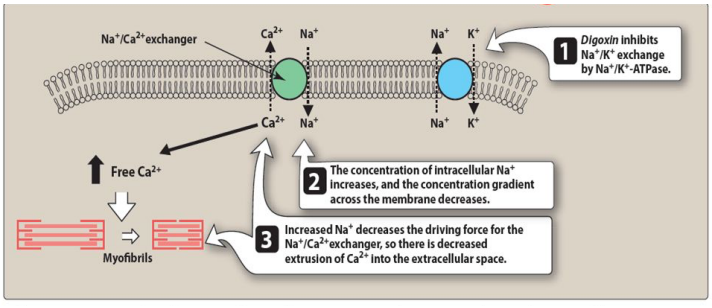
Positive Inotropic Agents

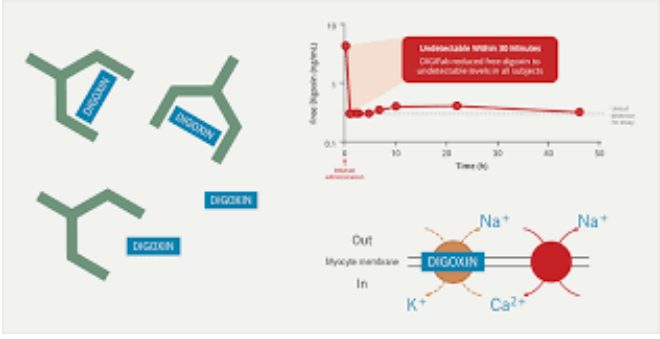
- MOA: increase contractility → increase CO
- NOTE: All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival; therefore, these agents, with the exception of digoxin, are only used for a short period mainly in the inpatient setting (ICU/CCU) in decompensated heart failure.



A. Digoxin

- MOA: Digoxin inhibits the Na^+/K^+ pump and reduces the ability of the myocardial fiber to actively pump Na^+ out of the cell → increases intracellular Ca levels → increase contractility → increases CO.
- Digoxin is not used in diastolic heart failure (HFpEF), since systolic function is intact.
- Digoxin also slows conduction velocity through the AV node, making it useful for atrial fibrillation.
- Therapeutic Application in HFrEF: Digoxin is indicated in patients with HFrEF who are symptomatic on optimal HF pharmacotherapy.
  - Digoxin is considered a 2nd line agent in HRrEF, used primarily in patients with a concomitant SVT, atrial fibrillation, or in patients with chronically low BP.
- Digoxin has a narrow therapeutic range, with only a small difference between a therapeutic dose and doses that are toxic.
  - A low serum drug concentration of digoxin (0.5-0.9 ng/mL) is beneficial in HFrEF, whereas in atrial fibrillation therapeutic serum drug conc of digoxin is 0.5-2.0 ng/ml.
- SEs: anorexia, nausea, vomiting, visual disturbances (blurred vision, or yellowish vision may be initial indicators of toxicity), bradycardia (d/t AV block).
- NOTE: hypokalemia predisposes a patient to digoxin toxicity, because digoxin competes with potassium for the same binding site on the Na^+/K^+-ATPase pump.
- NOTE: Digoxin should also be used with caution with other drugs that slow AV conduction, such as β-blockers, verapamil, and diltiazem.
- Digibind (digoxin immune Fab) is an antidote for digoxin toxicity → digoxin-specific antibody which binds and inactivates digoxin.

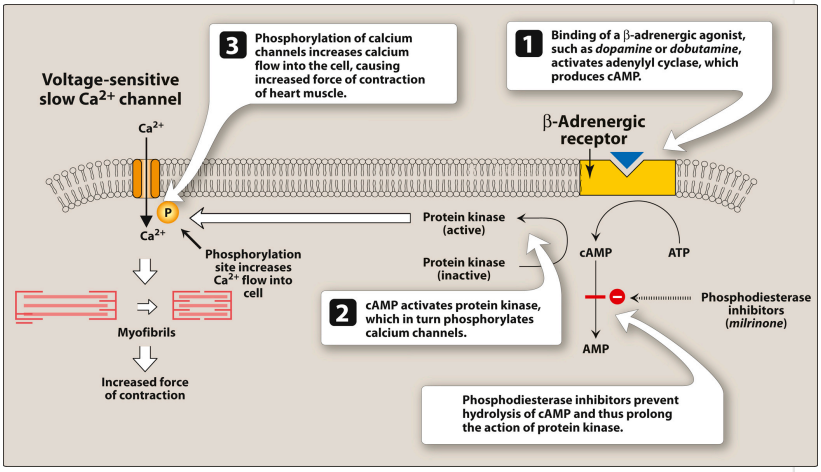




Positive Inotropic Agents (cont.)

B. β-Adrenergic agonists: Dobutamine

- MOA: Dobutamine improves cardiac performance by causing positive inotropic effects and vasodilation.
- β-Adrenergic agonists ultimately lead to increased entry of calcium ions into myocardial cells and enhanced contraction
- Dobutamine is administered as an IV infusion used as short-term treatment of acute decompensated HF in the hospital setting when cardiac output needs immediate augmentation.

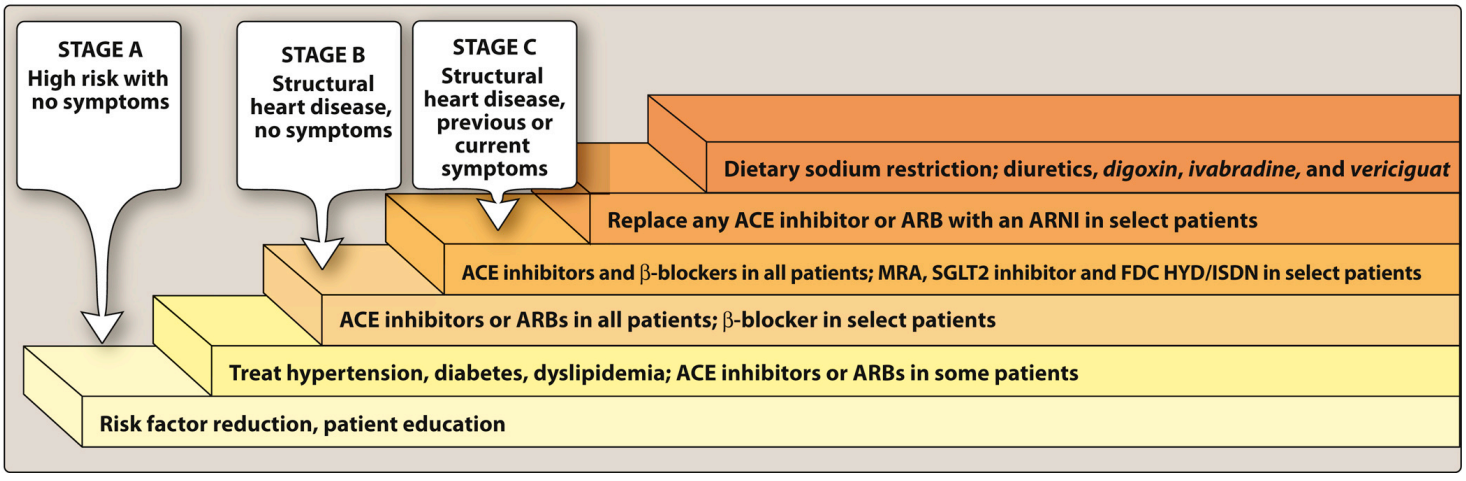


C. Phosphodiesterase inhibitors: Milrinone

- MOA: Milrinone increases the intracellular concentration of cAMP by inhibiting phosphodiesterase (PDE) → increases intracellular calcium → increases myocardial contractility.
- Milrinone is given by IV infusion for short-term treatment of acute decompensated HF with low cardiac output.

ORDER OF THERAPY

- Guidelines have classified chronic HF into four stages, from least to most severe.
- In patients with decompensated 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, β-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 a β-blocker after initial stabilization.
- Mineralocorticoid receptor antagonists, fixed-dose hydralazine and isosorbide dinitrate, and SGLT2 inhibitors are initiated in patients who continue to have HF symptoms despite optimal doses of an ACE inhibitor and β-blocker.
- If the patient remains symptomatic, either can be replaced by sacubitril/valsartan. Lastly, digoxin, ivabradine, and vericiguat are added for symptomatic benefit only in patients on optimal HF pharmacotherapy.



Preload & Afterload Reducing Agents

Predominantly Afterload Reduction (Arterial Dilators)

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

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

Predominantly Preload Reduction (Venous Dilators)

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

Mixed Afterload and Preload Reduction

(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)

Heart Failure

Mechanism

- Chronic activation of SNS & RAAS causes →
  - Remodeling of cardiac tissue
  - Loss of myocytes
  - Hypertrophy and fibrosis
- Triggers additional neurohormonal activation → if untreated results in death

Heart Failure

Compensatory Physiologic Response to HF

1. Increase sympathetic activity
2. Activation of RAAS
3. Activation of natriuretic peptide
4. Myocardial dysfunction

Heart Failure

Compensatory Physiologic Response to HF

1. Increase sympathetic activity
   - Baroreceptors sense decrease in BP
   - Activate SNS to sustain perfusion
   - Stimulate β-adrenergic receptors
   - ↑ inotropy and chronotropy
   - Vasoconstriction ↑ venous return and preload
   - ↑ preload will ↑ SV & cardiac output
   - In long term, cause decline in cardiac function

Heart Failure

Compensatory Physiologic Response to HF

2. Activation of RAAS
   - Drop in CO decreases blood flow to kidney
   - Activates RAAS
   - Results in ↑ peripheral resistance (afterload)
   - Retention of sodium & water
   - ↑ blood volume and venous return to the heart
   - If unable to pump extra volume → peripheral and pulmonary edema
   - ATII and aldosterone → cardio myocyte remodeling, fibrosis, inflammatory changes

Heart Failure

Compensatory Physiologic Response to HF

3. Activation of natriuretic peptide
   - ↑ in preload results in release of natriuretic peptides
   - Results in vasodilation, natriuresis
   - Inhibition of renin & aldosterone release
   - Reduction in myocardial fibrosis

Heart Failure

Compensatory Physiologic Response to HF

4. Myocardial dysfunction
   - Initial stretching of heart muscle → stronger contraction
   - Overstretch → weaker contraction
   - Known as “systolic failure” or HF with reduced EF

Heart Failure

Goal of medications in HF

- Increased cardiac contractility
- Reduce preload
- Normalize heart rate and rhythm

Heart Failure

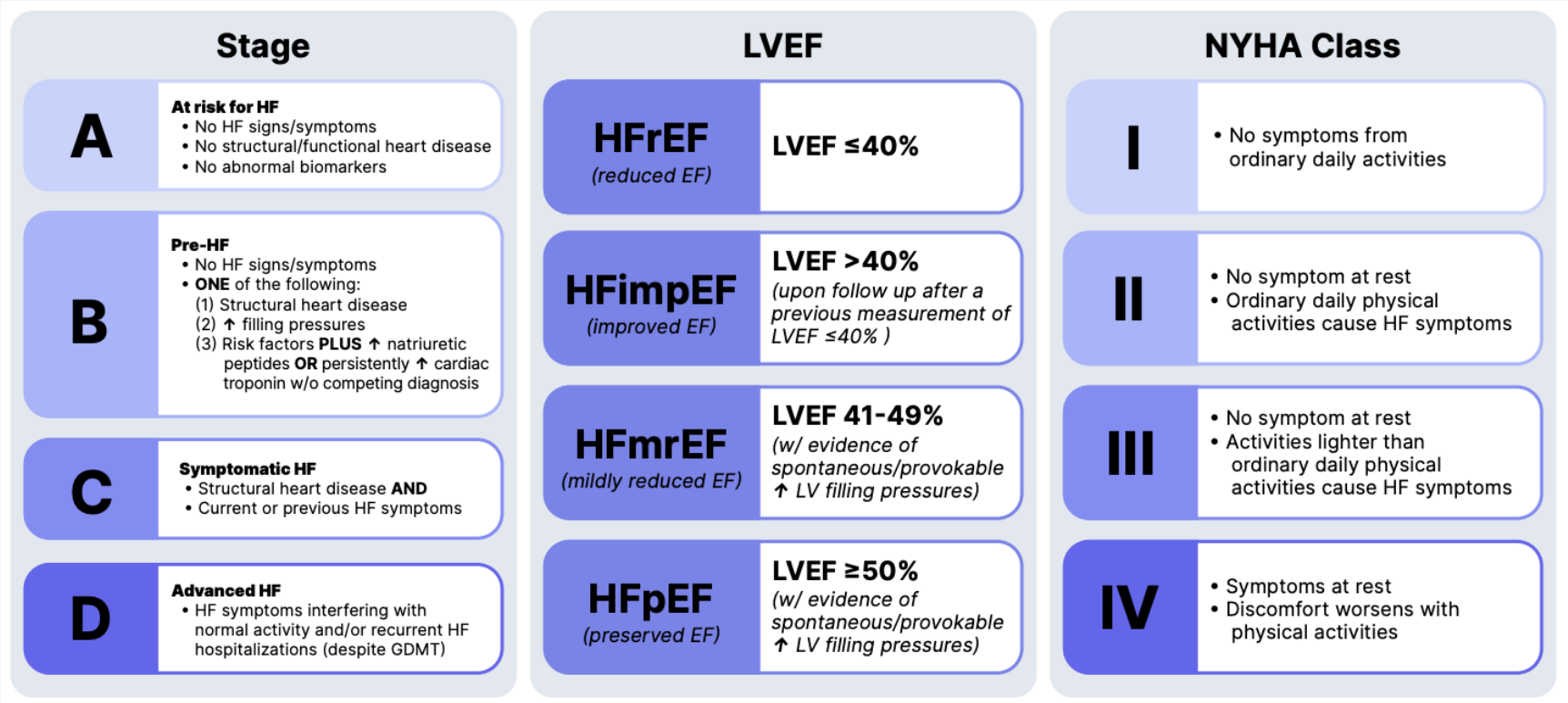
Medications

ACE-i	ARBs	ANRI	Aldosterone Antagonist	Beta-blocker	Diuretics	Vaso-venodilator	HCN channel blocker	Inotropic agent
Captoril Enalapril Ramipril Lisinopril Quinapril Fosinopril	Losartan Telmisartan Valsartan Candesartan	Sacubitril/Valsartan	Spironolactone Eplerenone	Bisoprolol Carvedilol Metoprolol succinate Metoprolol tartrate	Metolazone Furosemide Bumetanide Torsemide	Hydralazine Isosorbide dinitrate	Ivabradine	Digoxin Dobutamine MIlrinone

In HF, chronic activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), oxidative stress and inflammation, and resistance to natriuretic peptides are associated with remodeling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis. These create a vicious cycle that, if left untreated, leads to death.

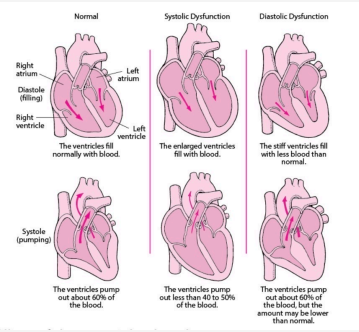
Heart Failure

Categories



Heart Failure

Pharmacotherapy Recommendations



Stage A

- Control BP in patients with hypertension
- SGLT2i in patients with T2DM **plus:**
  - Established CVD **or,**
  - High CV risk
- Manage existing comorbidities

Stage B

- ACEi and evidence-based BB in patients with LVEF ≤ 40%
  - If LVEF ≤ 40% **and recent MI**, use ARB if ACEi is not tolerated

Stage C (HFpEF)

- SGLT2i in **all patients** with HFpEF *(unless contraindicated)*
- May consider MRA and/or ARNi if LVEF < 55-60%
  - May consider regardless of LVEF for female patients
  - May consider ARB if unable to receive ARNi therapy
- PRN loop diuretic

Stage C (HFmrEF)

- PRN diuretics (**loop** preferred)
- SGLT2i may be beneficial
- May consider MRA, ACEi/ARB/ ARNi, and evidence-based BB *particularly* if LVEF is closer to **HFrEF threshold**

Stage C (HFimpEF)

- Continue GDMT
  - Even if asymptomatic

Heart Failure

Pharmacotherapy Recommendations

Stage C (HFrEF)

All patients

★ = 4 key drug classes of GDMT for HFrEF

- **RAASi (ARNi/ACEi/ARB)** ★
  - Order of preference: ARNi > ACEi > ARB
  - ARNi: NYHA class II-III*
  - ACEi or ARB: NYHA class II-IV
  - **36-hour washout** required when switching between ACEi and ARNi (and vice versa)
- **Beta-blocker** (evidence-based) ★
  - Bisoprolol, carvedilol, metoprolol succinate
- **MRA** (e.g., eplerenone, spironolactone) ★
  - NYHA class II-IV
  - eGFR >30 mL/min/1.73m2
  - Serum potassium <5 mEq/L
- **SGLT inhibitor** ★
  - Dapagliflozin, empagliflozin, sotagliflozin
  - With or without T2DM
- **Diuretics** (as needed)
  - Loop diuretics preferred

**The 2022 guideline recommendation on using an ARNi is limited to patients with NYHA class II-III symptoms. However, the 2024 ECDP for treating HFrEF recommends the use of an ARNi to those who can tolerate it (including those with NYHA class IV symptoms).*

Specific patients

- **Hydralazine + isosorbide dinitrate**
  - African American patients on GDMT
  - NYHA class III-IV; persistently symptomatic
- **Ivabradine**
  - NYHA class II-III and LVEF **≤35%**
  - On GDMT including **max tolerated BB**
  - In sinus rhythm with resting HR ≥70 BPM
- **Vericiguat**
  - NYHA class II-IV and LVEF **<45%**
  - Recent HF worsening
  - ↑ BNP or NT-proBNP
- **Digoxin**
  - If symptomatic despite GDMT **or**
  - Unable to tolerate GDMT
- **Potassium binders**
  - e.g., **Patiromer**, **sodium zirconium cyclosilicate**
  - Patients with hyperkalemia (K+ ≥5.5 mEq/L) while on RAASi
- **Omega-3 PUFA** (may consider as an adjunct)
  - NYHA class II-IV

Heart Failure

Pharmacotherapy Recommendations

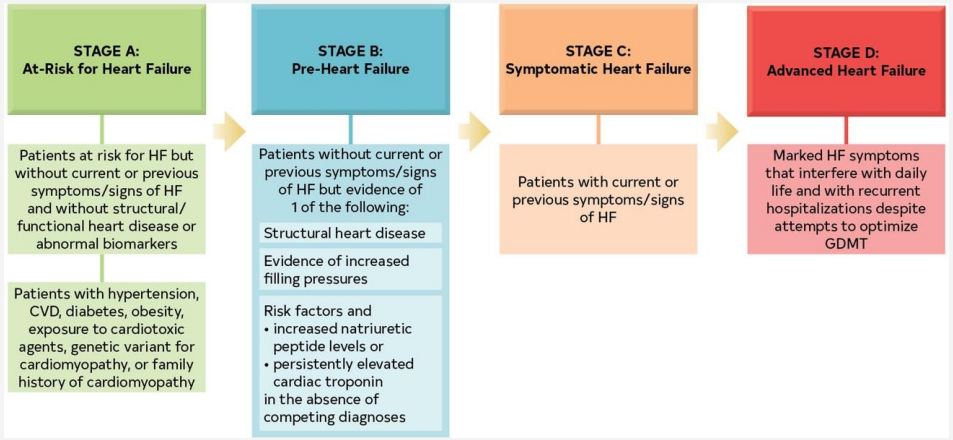
Selected Medications That May Cause or Exacerbate HF	
COX inhibitors (e.g., NSAIDs)	• ↑ H2O retention, ↑ vascular resistance, ↓ response to diuretics • **Immediate** onset, **major** induction/precipitation of HF
Thiazolidinediones	• Potential blockage of calcium channel • **Intermediate** onset, **major** induction/precipitation of HF
Saxagliptin, Alogliptin	• Mechanism is unclear • **Immediate or delayed** onset, **major** induction/precipitation of HF
Flecainide, Disopyramide	• Proarrhythmic, negative inotropic effects • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Sotalol	• Proarrhythmic effects, beta blockade • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Dronedarone	• Negative inotropic effects • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Doxazosin	• Beta-1 stimulation, ↑ renin and aldosterone • **Intermediate to delayed** onset, **moderate** induction/precipitation of HF
Diltiazem, Verapamil	• Negative inotropic effects • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Nifedipine	• Negative inotropic effects • **Immediate to intermediate** onset, **moderate** induction/precipitation of HF

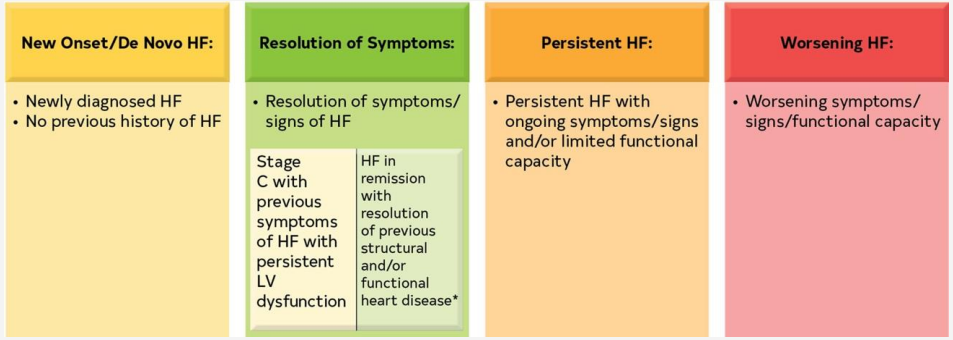
Recreated from Table 13 from the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

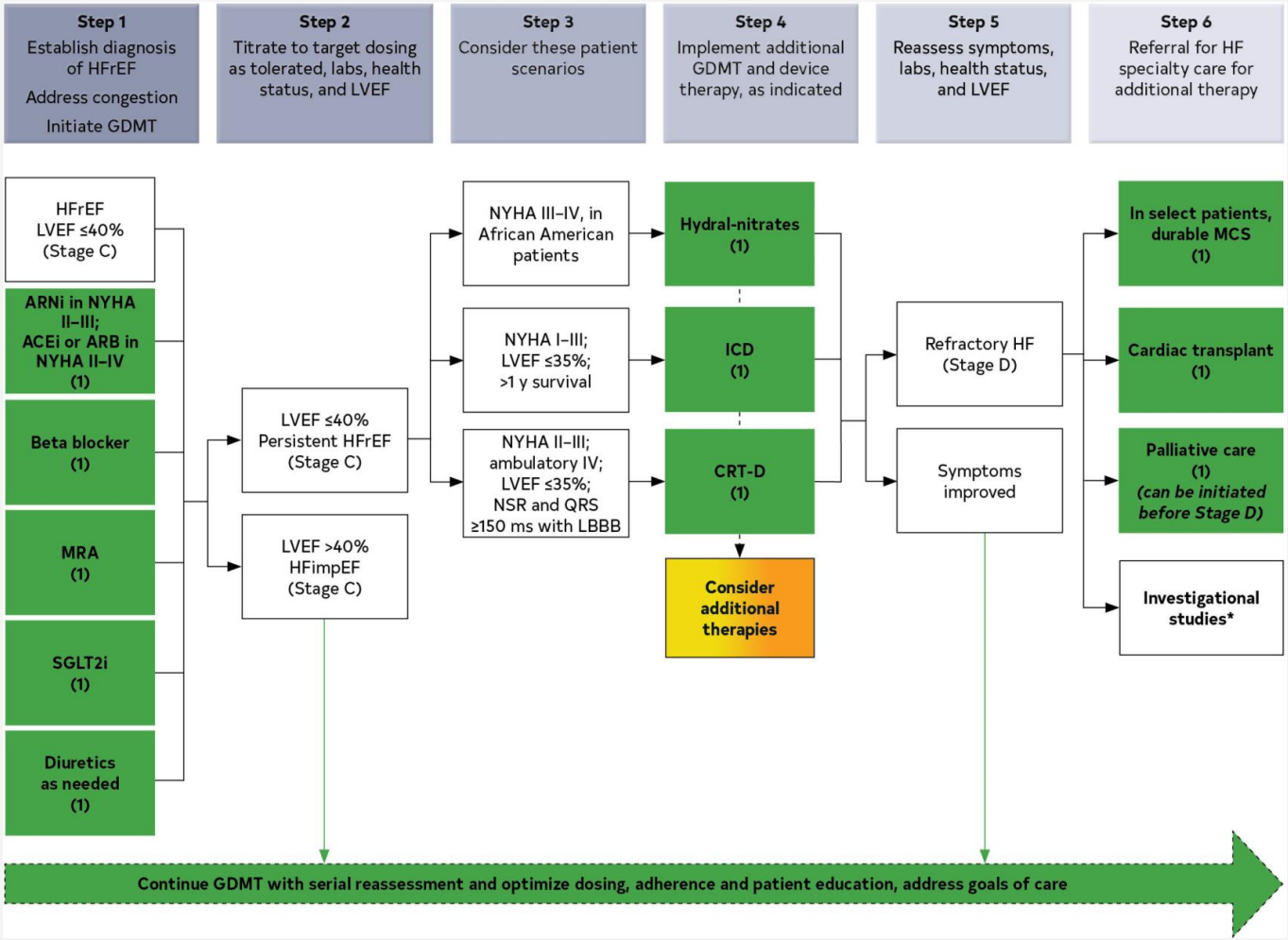
Heart Failure

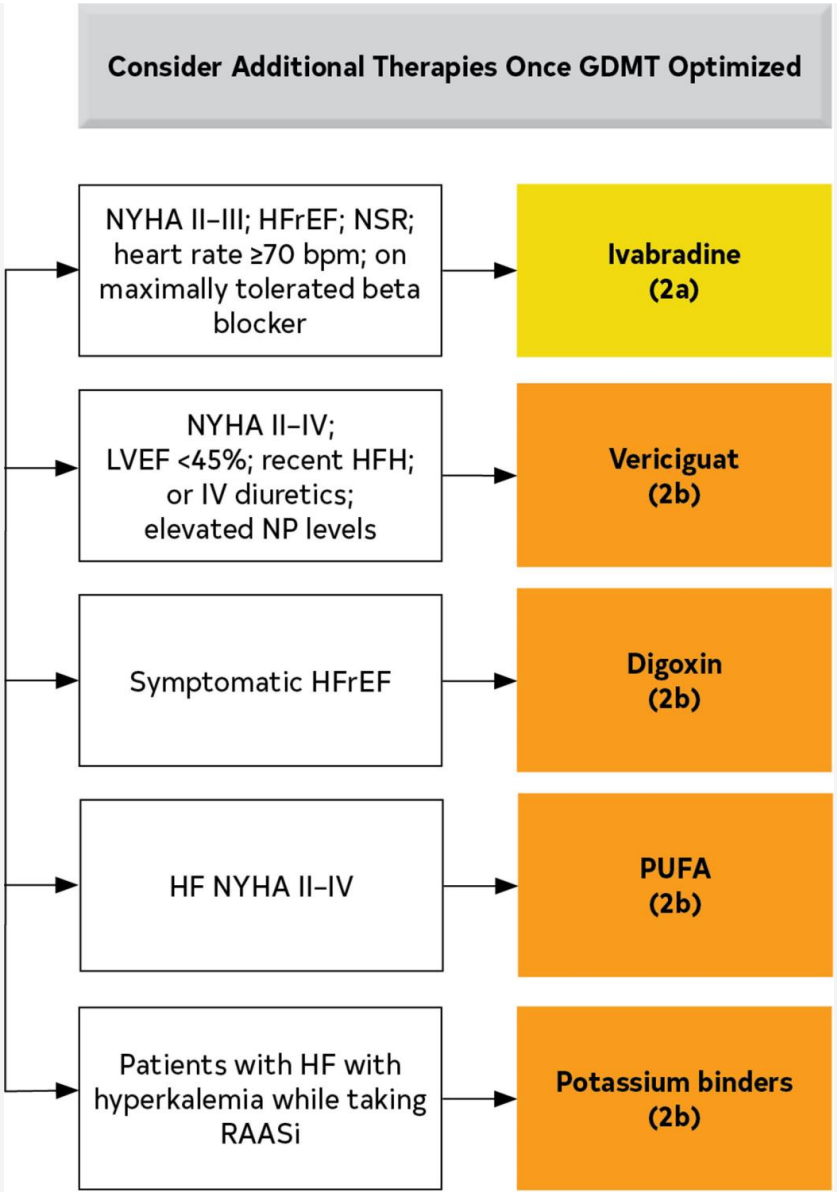
Treatment of HFrEF

- **ACC/AHA stage B**
  - Beta blocker
  - ACEI or ARB
- **ACC/AHA stages C and D**
  - Diuretic
  - RAAS inhibitors
  - Beta-blocker
  - SGLT-2 inhibitor
  - Mineralcorticoid receptor antagonists






Step 1
Establish diagnosis of HFrEF
Address congestion
Initiate GDMT
Step 2
Titrate to target dosing as tolerated, labs, health status, and LVEF
Step 3
Consider these patient scenarios
Step 4
Implement additional GDMT and device therapy, as indicated
Step 5
Reassess symptoms, labs, health status, and LVEF
Step 6
Referral for HF specialty care for additional therapy
HFrEF LVEF ≤40% (Stage C)
ARNi in NYHA II–III; ACEi or ARB in NYHA II–IV (1)
Beta blocker (1)
MRA (1)
SGLT2i (1)
Diuretics as needed (1)
LVEF ≤40% Persistent HFrEF (Stage C)
LVEF >40% HFimpEF (Stage C)
NYHA III–IV, in African American patients
NYHA I–III; LVEF ≤35%; >1 y survival
NYHA II–III; ambulatory IV; LVEF ≤35%; NSR and QRS ≥150 ms with LBBB
Hydral-nitrates (1)
ICD (1)
CRT-D (1)
Consider additional therapies
Refractory HF (Stage D)
Symptoms improved
In select patients, durable MCS (1)
Cardiac transplant (1)
Palliative care (1) (can be initiated before Stage D)
Investigational studies*
Continue GDMT with serial reassessment and optimize dosing, adherence and patient education, address goals of care


Consider Additional Therapies Once GDMT Optimized
NYHA II–III; HFrEF; NSR; heart rate ≥70 bpm; on maximally tolerated beta blocker
Ivabradine (2a)
NYHA II–IV; LVEF <45%; recent HFH; or IV diuretics; elevated NP levels
Vericiguat (2b)
Symptomatic HFrEF
Digoxin (2b)
HF NYHA II–IV
PUFA (2b)
Patients with HF with hyperkalemia while taking RAASi
Potassium binders (2b)

Heart Failure

Treatment of HFpEF

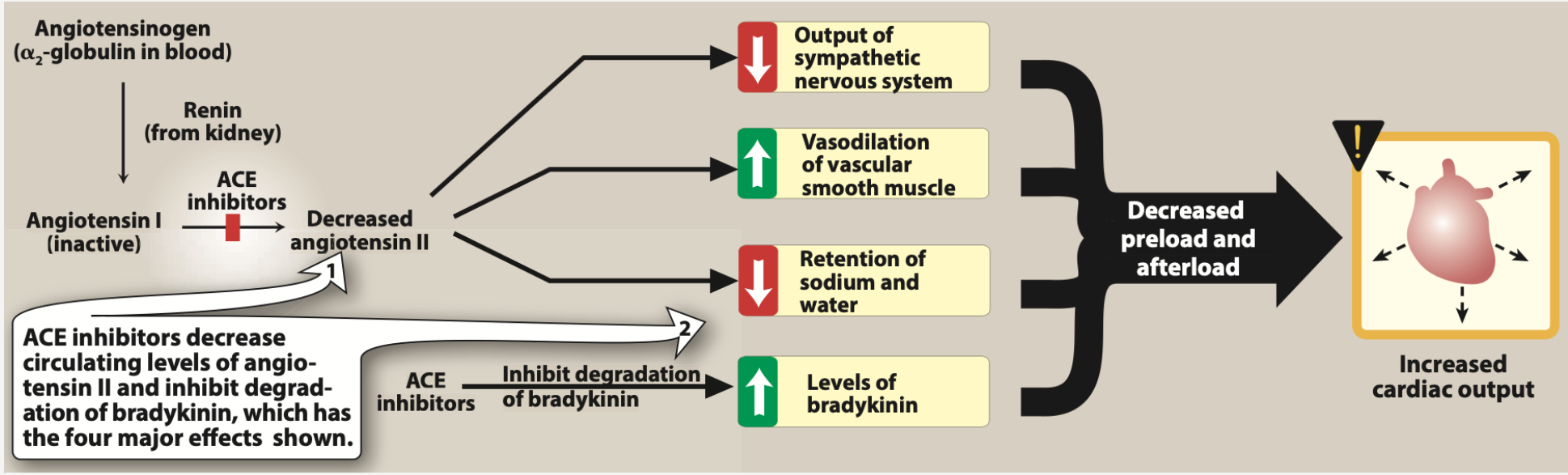
- First line
  - SGLT-2i
  - Loop diuretic if congestion
- Other agents
  - MRA
  - ARNI or ARB

Heart Failure

Medications to Avoid

- **Non-DHP CCB**
- **NSAIDs**
- **Thiazolidinediones (eg, pioglitazone)**
- **Antidepressants (eg, TCAs)**
- **Class III antiarrhythmic drugs**
- **DPP-4 inhibitors (eg, saxagliptin, alogliptin)**

ACEIs/ARBs


Angiotensinogen
(α_2-globulin in blood)
Renin
(from kidney)
Angiotensin I
(inactive)
ACE
inhibitors
Decreased
angiotensin II
1
2
ACE inhibitors decrease circulating levels of angiotensin II and inhibit degradation of bradykinin, which has the four major effects shown.
ACE
inhibitors
Inhibit degradation
of bradykinin
Output of
sympathetic
nervous system
Vasodilation
of vascular
smooth muscle
Retention of
sodium and
water
Levels of
bradykinin
Decreased
preload and
afterload
Increased
cardiac output

Heart Failure Medications

ACEIs/ARBs

"-prils" and "-sartans"

Indication

- HFrEF (1st line) – asymptomatic and symptomatic
- HFpEF (adjunct)
- Hypertension
- ACS

Heart Failure Medications

ACEIs/ARBs

"-prils" and "-sartans"

MoA

- Discussed previously
- Decrease
  - SVR
  - PCWP
  - RAP
  - End diastolic and systolic dimensions
- Reverse remodeling in myocytes that cause progression of HF

Heart Failure Medications

ACEIs/ARBs

"-prils" and "-sartans"

Adverse Effects

- Hyperkalemia
- Worsening of renal failure in AKI
- Dry cough (ACEIs)
- Angioedema (rare)

Heart Failure Medications

ACEIs/ARBs

"-prils" and "-sartans"

Contra-indications

- Co-administration of ACEIs and ARBs
- Exception is Entresto (sacubitril/valsartan)
- Pregnancy (teratogenic)

Beta-Blockers

Heart Failure Drugs

Beta-Blockers

"-ololS"

Indications

- HFrEF stage B or higher
  [carvedilol, metoprolol succinate, bisoprolol]
- HTN
- Arrhythmias
- Angina

Heart Failure Drugs

Beta-Blockers

"-ololS"

MoA

- In HF, SNS is overstimulated → increases NE
- Results in cardiac remodeling, arrhythmias, death
- Reduce morbidity and mortality in HFrEF

Heart Failure Drugs

Beta-Blockers

"-ololS"

Adverse Effects

- Decreased inotropy
- Bradycardia
- Use with caution with non-DHP CCB, amiodarone

Contra-indications

- Acute CHF exacerbation (hemodynamically unstable, volume overloaded)

Diuretics

Heart Failure Drugs

Loop Diuretic

(eg, furosemide)

Indications

- Volume overload in HFrEF and HFpEF
- For HFrEF, if stage C or D
- HFrEF with NYHA II-IV and EF <35%
- No mortality benefit in HF, unlike BB, ACEi/ARB, aldosterone antagonists

Heart Failure Drugs

Aldosterone antagonists

(eg, spironolactone, eplerenone)

Indication

- HFrEF (symptomatic or if recent MI)

Heart Failure Drugs

Aldosterone antagonists

(eg, spironolactone, eplerenone)

MoA

- Inhibitors of aldosterone at mineralcorticoid receptor
- Prevent salt retention, myocardial hypertrophy, hypokalemia

Heart Failure Drugs

Aldosterone antagonists

(eg, spironolactone, eplerenone)

Adverse Effects

- Gynecomastia (spironolactone has affinity for androgen and progesterone receptors)

Hydralazine/ Isosorbide Dinitrate

Heart Failure Medications

Hydralazine & Isosorbide Dinitrate

Indications

- African-American with HFrEF NYHA III-IV who are already on beta-blockers and ACEi/ARB

Heart Failure Medications

Hydralazine & Isosorbide Dinitrate

MoA

- Hydralazine
  - Afterload reduction (arterial vasodilation)
  - Reflexively increases heart rate
- Nitrates
  - Decrease preload (venous vasodilation)
  - Decreased afterload (arterial vasodilation)

Heart Failure Medications

Hydralazine & Isosorbide Dinitrate

Adverse Effects

- Nausea, dizziness, headaches [hydralazine and nitrates]
- Hepatotoxicity, drug-induced lupus [hydralazine]

Contra-indication

- Coadministration of PDE-5 inhibitor

Digoxin

Heart Failure Medications

Digitalis glycosides

Digoxin

Indications

- HFrEF
  - Not first line
  - Used if initial therapies ineffective and patient symptomatic
  - No mortality benefit

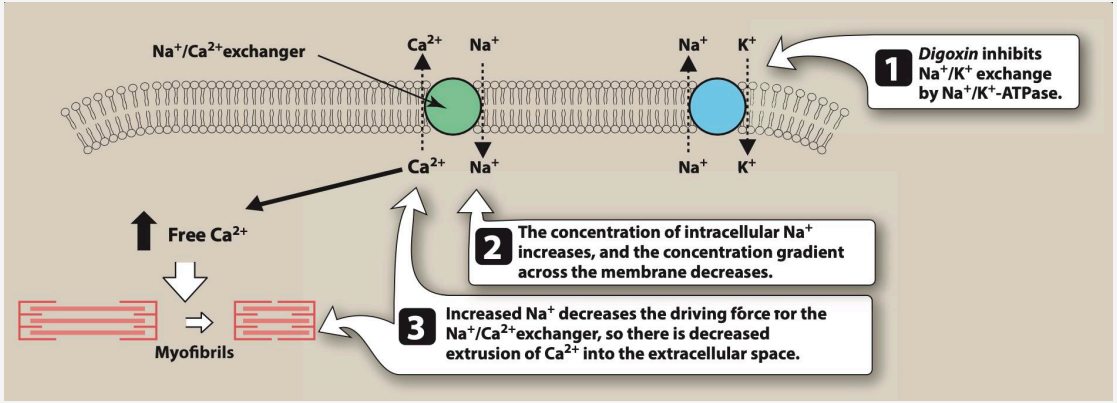
Heart Failure Medications

Digitalis glycosides

Digoxin

MoA

- Inhibits Na+ K+ ATPase
- Leads to increased intracellular Na+ and Ca2+
- Weak positive inotrope and negative chronotropic agent



Heart Failure Medications

Digoxin

Adverse Effects

- Bradycardia
- Digitalis toxicity if impaired renal function
  - Nausea, vomiting, blurry vision, confusion
  - EKG changes – bradycardia, T wave inversion or flattening

Contraindications

- Ventricular fibrillation

Sacubitril/Valsartan

Heart Failure Medications

Sacubitril/Valsartan

ARNI (sacubitril)/ARB(valsartan)

Indication

- HFrEF NYHA II-IV
- First available angiotensin receptor-neprilysin inhibitor

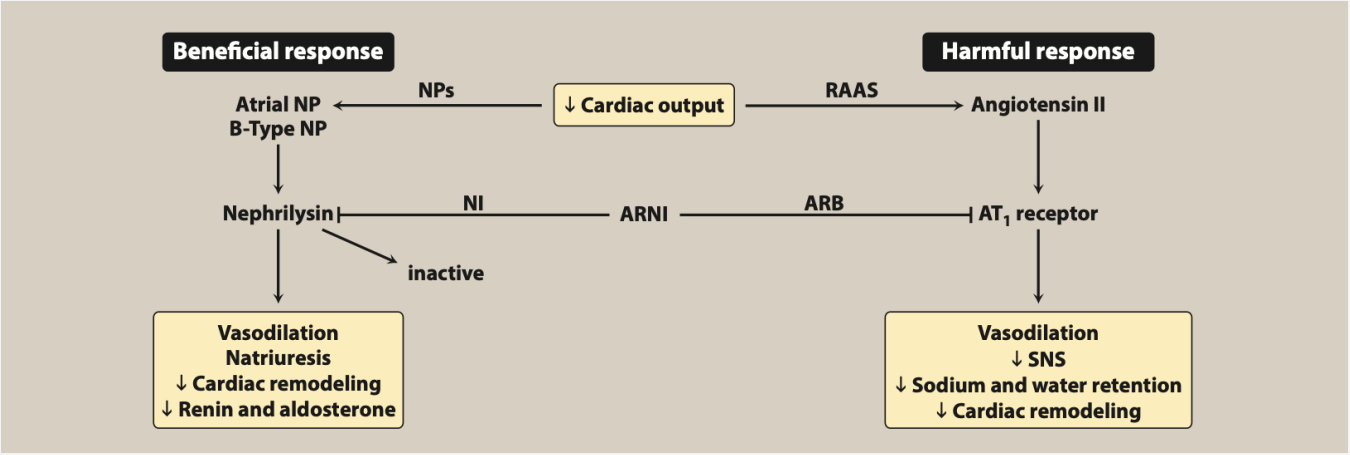
Heart Failure Medications

Sacubitril/Valsartan

ARNI (sacubitril)/ARB(valsartan)

MoA

- Inhibits neprolysin (enzyme that lowers natrieuretic peptides and vasoactive peptides)



Heart Failure Medications

Sacubitril/Valsartan

ARNI (sacubitril)/ARB(valsartan)

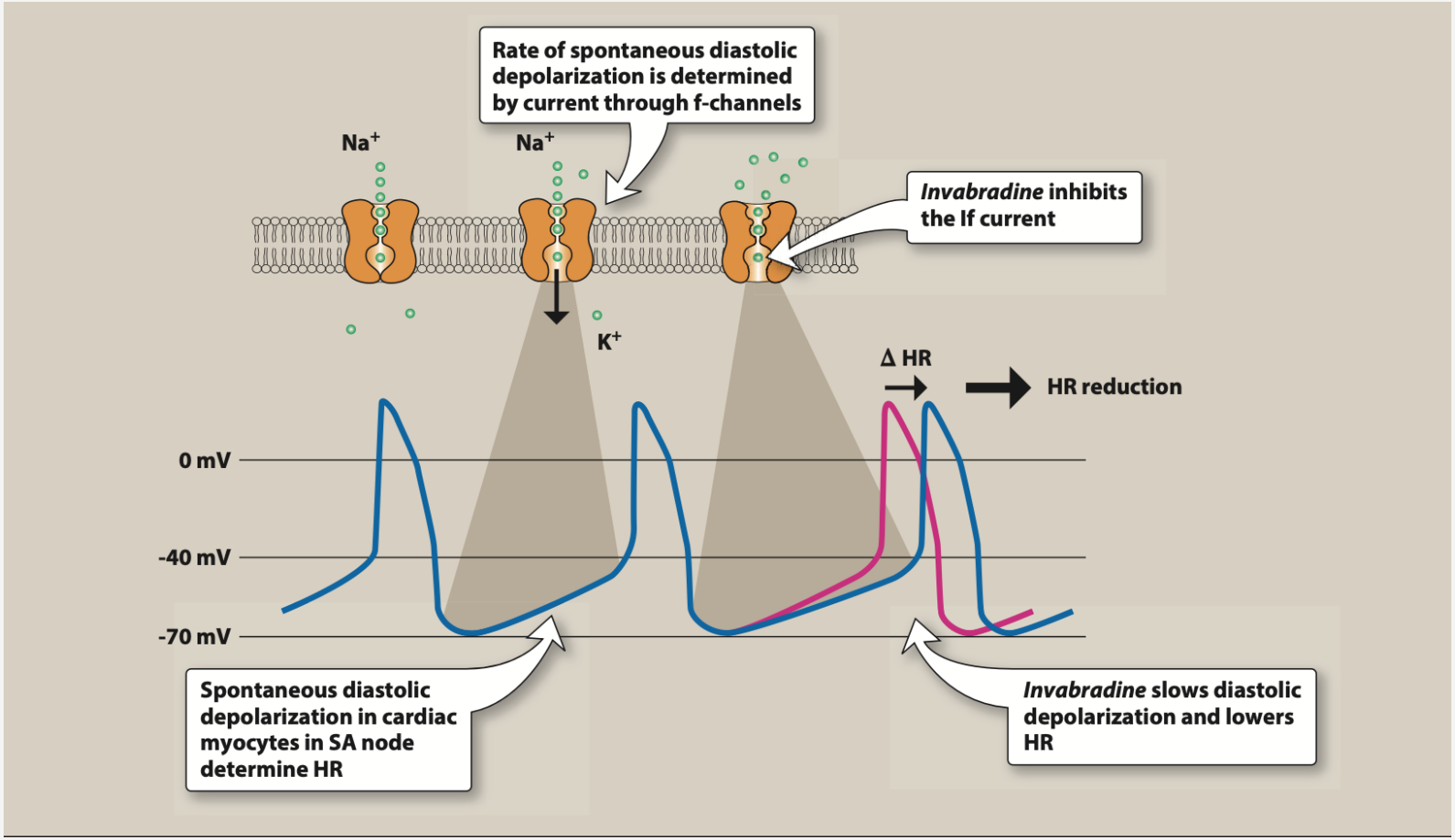
Adverse Effect

- Hyperkalemia
- Hypotension
- Cough, renal failure, angioedema

Contra-indications

- Pregnancy
- History of angioedema with prior ACEi/ARB
- Recent ACEIs in past 36h

Ivabradine


Rate of spontaneous diastolic depolarization is determined by current through f-channels
Na+
Na+
Invabradine 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
Invabradine slows diastolic depolarization and lowers HR

Heart Failure Medications

Ivabridine

Indication

- HFrEF NYHA II-III

Heart Failure Medications

Ivabridine

MoA

- Inhibits HCN channel → inhibits current through SA node
- Decreases heart rate (SA node)
- Doesn't affect contractility

Heart Failure Medications

Ivabridine

Adverse Effects

- Atrial fibrillation
- Bradycardia

Drug interactions

- CYP3A4 inhibitors or inducers
- Pregnancy or breast-feeding

Heart Failure Medications

Ivabridine

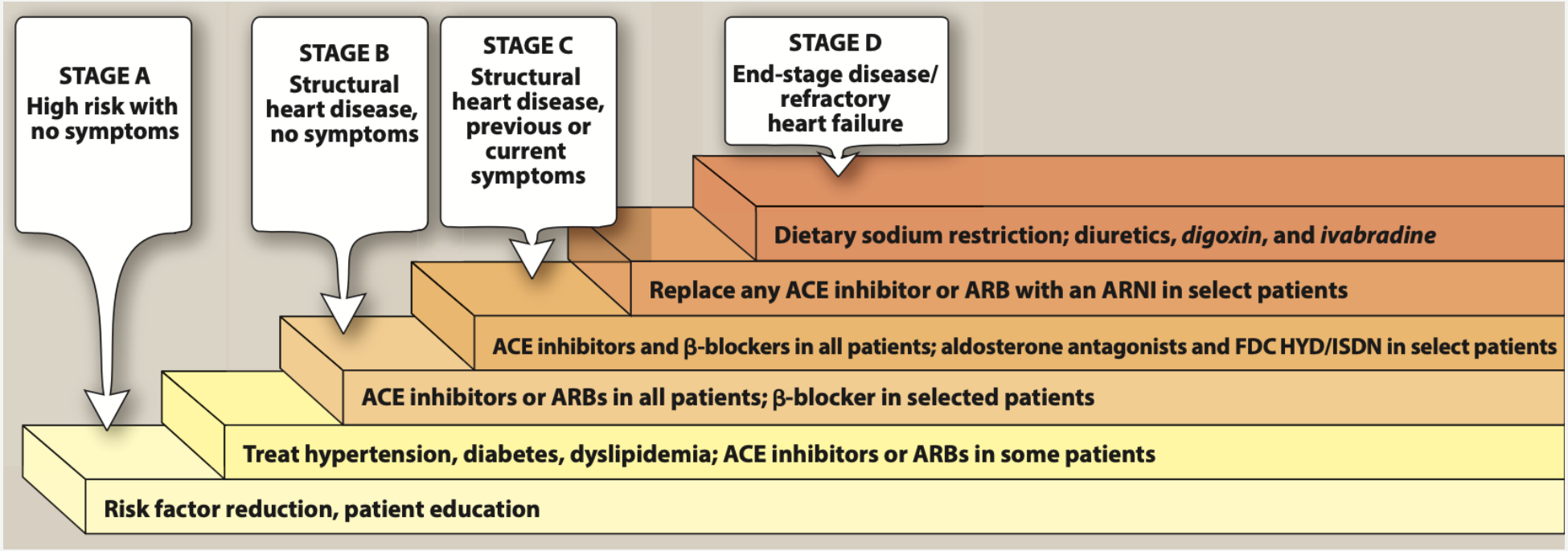
Contra-indications

- Decompensated HF
- HR <60
- Hepatic impairment
- Sick sinus syndrome, SA block, 3rd degree AV block

Heart Failure

Management

Class I	Symptoms of heart failure only at levels that would limit normal individuals—that is, ordinary physical activity does not cause symptoms.
Class II	The patients are comfortable at rest; symptoms of heart failure appear on ordinary exertion.
Class III	Symptoms of heart failure on less-than-ordinary exertion; marked limitations of physical activity
Class IV	Symptoms of heart failure at rest; unable to carry on any physical activity without HF symptom



Problem Based Learning

PBL Q1

A patient is newly diagnosed with HFrEF and is asymptomatic. Which is the most appropriate drug to initiate for symptomatic and survival benefits?

A. Dobutamine
B. Furosemide
C. Lisinopril
D. Sacubitril/valsartan

PBL Q2

Which of the following statements best describes the action of ACE inhibitors on the failing heart?

A. ACE inhibitors increase vascular resistance.

B. ACE inhibitors decrease cardiac output.

C. ACE inhibitors reduce preload.

D. ACE inhibitors increase aldosterone.

PBL Q3

A Hispanic man with HFrEF is currently takes maximally tolerated doses of metoprolol succinate and enalapril, along with moderate dose furosemide. He is euvolemic, but continues to have HF symptoms. The systolic blood pressure is low, but the patient does not have signs or symptoms of hypotension. Which is the best recommendation to improve HF symptoms and survival in this patient?

A. Stop enalapril, wait 36 hours, and start sacubitril/valsartan.

B. Start digoxin.

C. Start fixed-dose hydralazine and isosorbide dinitrate.

D. Start spironolactone.

PBL Q4

B-Blockers improve cardiac function in HF by

A. decreasing cardiac remodeling.

B. increasing heart rate.

C. increasing renin release.

D. activating norepinephrine.

PBL Q5

A 70-year-old woman has HFrEF, hypertension, and atrial fibrillation. She takes hydrochlorothiazide, lisinopril, metoprolol tartrate, and warfarin. She feels well and has no cough, shortness of breath, or edema. Which of the following changes is most appropriate for her drug therapy?

A. Discontinue hydrochlorothiazide.

B. Change lisinopril to losartan.

C. Decrease warfarin dose.

D. Change metoprolol tartrate to metoprolol succinate.

PBL Q6

A 75-year-old white man has HFrEF and reports stable HF symptoms. His current drug therapy includes optimal dose enalapril, carvedilol, and spironolactone. Which is the best recommendation to improve HF symptoms and survival?

A. Start fixed-dose hydralazine/isosorbide dinitrate.
B. Start ivabradine.
C. Replace enalapril with sacubitril/valsartan.
D. Start digoxin.

PBL Q7

How is spironolactone beneficial in HF?

A. Promotes potassium secretion

B. Acts as aldosterone agonist

C. Prevents cardiac hypertrophy

D. Decreases blood glucose

PBL Q8

Which of the following is important to monitor in patients taking digoxin?

A. Chloride

B. Potassium

C. Sodium

D. Zinc

PBL Q9

Which of the following describes the mechanism of action of milrinone in HF?

A. Decreases intracellular calcium

B. Increases cardiac contractility

C. Decreases cAMP

D. Activates phosphodiesterase

PBL Q9

A 52 year-old African American woman who has HFrEF is seen in clinic today reporting stable HF symptoms, but is having occasional peripheral brightness. Otherwise vision is unchanged. Current medication regimen includes sacubitril/valsartan, carvedilol, fixed-dose hydralazine and isosorbide dinitrate, ivabradine, and bumetanide. Which is the best recommendation to minimize the adverse effect of peripheral brightness?

A. Stop all HF medications immediately.
B. Discontinue sacubitril/valsartan only.
C. Do nothing; this adverse effect will slowly
D. improve over time.
E. Reduce the dose of ivabradine.

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2. Golan DE, Armstrong EJ, Armstrong AW, eds. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. 4. Edition. Wolters Kluwer; 2017.
3. Papadakis, M., Rabow, M., McQuaid, K., & Gandhi, M. (2024). CURRENT medical diagnosis and treatment 2025 (64th ed.). Columbus, OH: McGraw-Hill Education.
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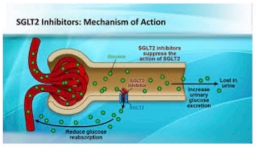
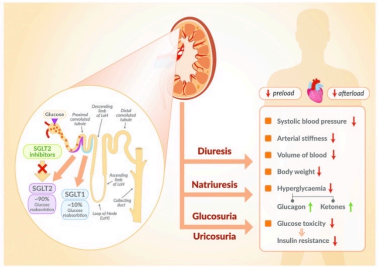
SGLT-2 (Sodium-Glucose Cotransporter-2) Inhibitors: Dapagliflozin (Farxiga) and Empagliflozin (Jardiance)



- 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 and Uricosuria
    - → decrease in 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 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).

Preload & Afterload Reducing Agents

Predominantly Afterload Reduction (Arterial Dilators)

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

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

Predominantly Preload Reduction (Venous Dilators)

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

Mixed Afterload and Preload Reduction

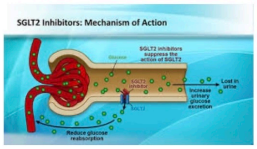
(1) ACE-Inhibitors
- Captopril (Capoten)
- Enalapril (Vasotec)
- Lisinopril (Prinivil, Zestril)

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

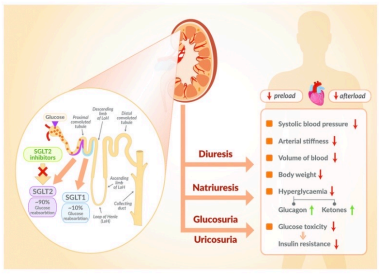
(3) SGLT-2 Inhibitors
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

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

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 and Uricosuria
    - → decrease in 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 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).

Non-Pharmacologic Inventions

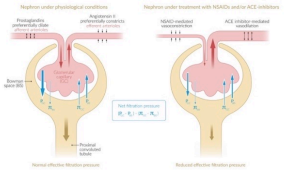
A. Elimination of Drugs that may Induce Heart Failure

(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

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.

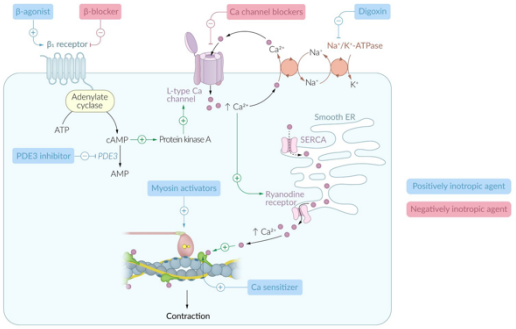
Systolic Heart Failure (continued)

- 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.

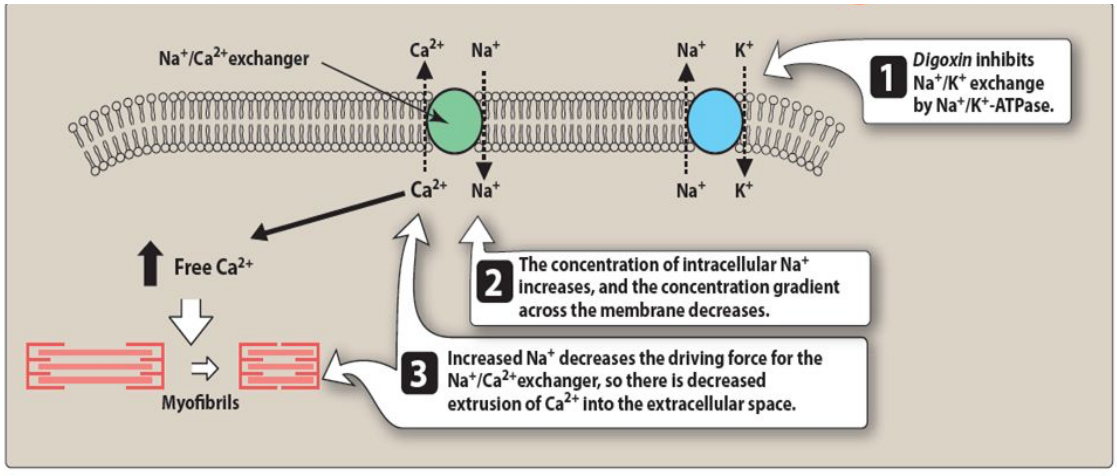
- **Summary of Primary Agents Used in Systolic Heart Failure** (UpToDate 2024)

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	

- **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.

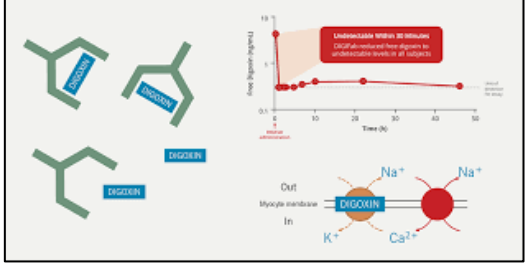


    - Digoxin is not used in diastolic heart failure (HFpEF), since systolic function is intact.



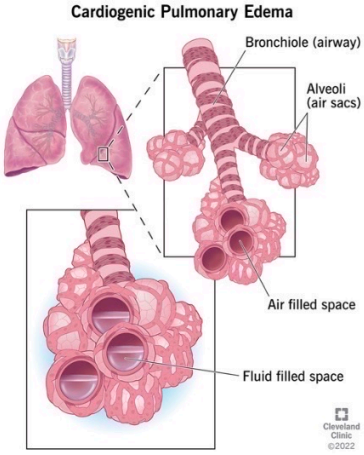
  - Digoxin Adverse Effects → most prevalent when serum digoxin levels are > 2 mcg/L or when serum K < 3.0 mEq/L (normal: 3.5-5.2 mEq/L).
    - Cardiac: bradycardia (HR < 50) due to AV block
    - GI: anorexia, nausea/vomiting
    - Visual disturbances: altered color perception, haloes
    - Fatigue/Weakness
    - 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

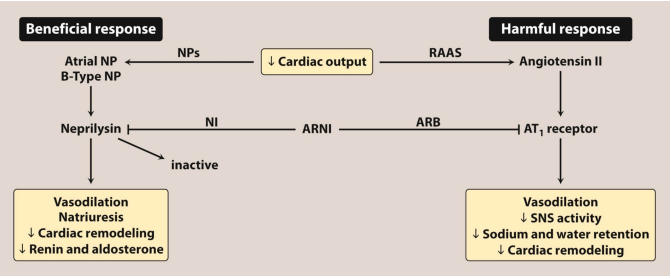
Digoxin Immune Fab (Digibind)



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)




Beneficial response
Harmful response
NPs
↓ Cardiac output
RAAS
Atrial NP
B-Type NP
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

SGLT2 inhibitors reduce plasma volume through glucosuria and natriuresis, thereby lowering preload and afterload. Although the mechanism is not fully understood, 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.

Dapagliflozin and empagliflozin

SGLT2 inhibitors, such as dapagliflozin [dap-a-gli-FLOE-zin] and empagliflozin [em-pa-gli-FLOE-zin], reduce the development of HF in patients with a history of diabetes and reduce the risk of HF hospitalization and cardiovascular death in those with HFrEF.

1. Actions

SGLT2 inhibitors mainly inhibit SGLT2 in the proximal tubule to reduce reabsorption of glucose and sodium. As such, they increase urinary glucose and sodium excretion, resulting in glucosuria, lower blood glucose, and natriuresis. Compared with diuretics, SGLT2 inhibitors may selectively reduce interstitial volume versus intravascular volume, thus limiting reflexive neurohormonal stimulation. Although there are multiple possible mechanisms responsible for the cardioprotective effects of SGLT2 inhibitors, the most plausible theory is inhibition of the sodium–hydrogen exchanger (NHE) prevents calcium overload and further contributes to natriuresis.

2. Therapeutic use

SGLT2 inhibitors should be considered in patients with symptomatic HFrEF who are on optimal HF pharmacotherapy with β-blockers, ACE inhibitors, and MRAs. Due to the natriuretic effects of SGLT2 inhibitors, dosages of diuretics may need to be titrated down following initiation of SGLT2 therapy. SGLT2 inhibitors are also indicated for patients with type 2 diabetes due to their enhanced excretion of glucose (see Chapter 24).

3. Pharmacokinetics

Dapagliflozin and empagliflozin are well absorbed and may be administered with and without food. Both are mainly metabolized via glucuronidation and exhibit minimal pharmacokinetic interactions. Parent drug and inactive metabolites are renally excreted. A similar half-life of approximately 12 hours for each allows for once-daily dosing.