College of Pharmacy
Fourth year. Clinical Pharmacy
Cardiovascular disorders

Heart Failure

Introduction

1-Heart failure (HF) is a **syndrome associated with signs and symptoms due to abnormalities in cardiac structure or function**

2-HF may be caused by an abnormality in **systolic function**, **diastolic function, or both**.

3-HF with reduced systolic function (ie, reduced left ventricular ejection fraction, LVEF) is referred to as **HF with reduced ejection fraction (HFrEF**).

4-Diastolic dysfunction **with normal LVEF** is termed **HF with preserved ejection fraction** (**HFpEF**).

Pathophysiology

1-**Causes of systolic dysfunction** (decreased contractility) include reduced muscle mass (eg, myocardial infarction [MI])

2-**Causes of diastolic dysfunction** (restriction in ventricular filling) include increased ventricular stiffness, and ventricular hypertrophy.

3-The leading causes of HF are **coronary artery disease and hypertension**.

4-Decreased cardiac output (CO) results **in activation of compensatory responses to maintain circulation:**

> (A) **Tachycardia** and **increased contractility** through sympathetic nervous system activation, (B) Increased preload (through **sodium and water retention**) increases **stroke volume**, (C) **vasoconstriction**, and (D) **ventricular hypertrophy and remodeling**.

5-Although these compensatory mechanisms **initially maintain cardiac function**, they are **responsible for the symptoms of HF and contribute to disease progression**.

6-**Chronic activation of the neurohormonal systems** results in a cascade of events that **affect the myocardium**.

7-These events lead to **changes** in ventricular **size** (left ventricular hypertrophy), **shape**, **structure**, and **function** known as **ventricular remodeling.**

Clinical presentation

1-Patient presentation may range from asymptomatic to cardiogenic shock. **Primary symptoms are** dyspnea (especially on exertion) and fatigue, which lead to exercise intolerance.

2-**Other pulmonary symptoms include:** orthopnea, paroxysmal nocturnal dyspnea (PND), tachypnea, and cough. Fluid overload can result in pulmonary congestion and peripheral edema.

3-**Nonspecific symptoms may include** fatigue, nocturia, hemoptysis, abdominal pain, anorexia, nausea, bloating, ascites, poor appetite or early satiety, and weight gain or loss.

Diagnosis

1-**Ventricular hypertrophy** can be demonstrated on **chest radiograph** or **electrocardiogram** (**ECG**). Chest radiograph may also show pleural effusions or pulmonary edema.

2-**Echocardiogram** can quantify LVEF to determine if systolic or diastolic dysfunction is present.

3-The New York Heart Association Functional **Classification System** is intended primarily to classify symptoms according to the physician's subjective evaluation.

- **Functional class (FC)-I** patients have no limitation of physical activity.
- **FC-II** patients have slight limitation.
- **FC-III** patients have marked limitation
- **FC-IV** patients are unable to carry on physical activity without discomfort.

Treatment of chronic heart failure

Goals of Treatment: Improve quality of life, relieve or reduce symptoms, prevent or minimize hospitalizations, slow disease progression, and prolong survival.

General Approach

1-The first step is to **determine the etiology or precipitating factors**. Treatment of underlying disorders (e.g., hyperthyroidism) may obviate the need for treating HF.

2-An international group developed a staging system:

Stage	Description	Recommendation
Stage A	**At risk for HF** (No HF signs or symptoms with No structural heart disease)	Drugs are recommended for HF prevention in select patients
Stage B	**PreHF** (No HF signs or symptoms but with structural heart disease)	Drugs are recommended for HF prevention in select patients
Stage C	**HF** (HF signs or symptoms with structural heart disease)	Most patients with HFrEF in stage C should receive **Guideline directed medical therapy (GDMT)** proven to reduce morbidity and mortality.
Stage D	**Advanced HF** (persistent HF symptoms despite maximally tolerated GDMT)	They should be considered for specialized interventions, including mechanical circulatory support, continuous IV positive inotropic therapy, or cardiac transplantation

Nonpharmacologic Therapy of Chronic Heart Failure

1-Interventions include **restriction of fluid intake and dietary sodium intake** (<2–3 g of sodium/day) with daily weight measurements.

2-In patients with hyponatremia or persistent volume retention despite high diuretic doses and sodium restriction, **limit daily fluid intake** to 2 L/day from all sources.

3-**Revascularization** or anti-ischemic therapy in patients with **coronary disease** may reduce HF symptoms. **Drugs that can aggravate HF should be discontinued if possible**.

Pharmacologic Therapy for Stage C HFrEF

1-In general, patients with stage C HFrEF should receive an **ACE inhibitor**, **ARB**, or **ARNI** **along with β-blocker**, **Sodium Glucose Cotransporter Type 2 (SGLT2) Inhibitors** [4] plus an **aldosterone antagonist**.

2-Administer a **diuretic if there is evidence of fluid retention**. A **hydralazine–nitrate combination, ivabradine, Vericiguat or digoxin may be considered in select patients.**

A-Diuretics

1-**Diuretic** therapy (in addition to sodium restriction) is recommended **for all patients with clinical evidence of fluid retention.**

2-However, because they **do not alter disease progression or prolong survival**, diuretics are not required for patients without fluid retention.

3-**Thiazide** diuretics (eg, hydrochlorothiazide) are relatively weak and **are infrequently used alone in HF**. However, thiazides or the thiazide-like diuretic metolazone can be used **in combination with a loop** diuretic to promote very effective diuresis.

4-**Thiazides** may be preferred over loop diuretics in patients with only **mild fluid retention and elevated BP** because of their more persistent antihypertensive effects.

5-**Loop diuretics** (furosemide, bumetanide, and torsemide) are **usually necessary** to restore and maintain euvolemia in HF.

6-Unlike thiazides, loop diuretics **maintain their effectiveness in the presence of impaired renal function**, although higher doses may be necessary.

7-**Adverse effects of diuretics** include hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, and renal dysfunction.

B-Angiotensin-Converting Enzyme Inhibitors

1-ACE inhibitors improve symptoms, slow disease progression, **and decrease mortality** in patients with HFrEF.

2-**Prior guidelines** recommended that all patients with HFrEF, regardless of whether or not symptoms are present, should receive an ACE inhibitor to reduce morbidity and mortality, unless there are contraindications. However, **recent evidence** suggests that **sacubitril/valsartan is preferred over ACE inhibitors** (or **ARBs**) **for HFrEF** unless other circumstances (eg, affordability) are present in individual patients.

3-Although symptoms may improve within a few days of starting therapy, **it may take weeks to months before the full benefits are apparent**.

4-**The most common adverse effects include** hypotension, renal dysfunction, and hyperkalemia. A dry, nonproductive cough (occurring in 15%–20% of patients) is the most common reason for discontinuation.

5-Because **cough is a bradykinin-mediated effect**, replacement with sacubitril/valsartan or an ARB is reasonable; however, caution is required because **crossreactivity** has been reported.

6-**Angioedema** occurs in approximately 1% of patients and **is potentially life threatening**; ACE inhibitors are contraindicated in patients with a history of angioedema.

7-ACE inhibitors are **contraindicated in pregnancy** due to various congenital defects.

C-Angiotensin Receptor Blockers

1-Because they do not affect the ACE enzyme, ARBs do not affect bradykinin, which is **linked to ACE inhibitor cough and angioedema**.

2-Although ARBs are a guideline recommended alternative in patients who are unable to tolerate an ACE inhibitor due to cough or angioedema, **sacubitril/valsartan is preferred for ACE inhibitor associated cough.**

3-Although numerous ARBs are available, **only candesartan, valsartan, and losartan** are **recommended in the guidelines** because efficacy has been demonstrated in clinical trials.

4-ARBs are **not suitable alternatives in patients with hypotension, hyperkalemia, or renal insufficiency due to ACE inhibitors** because they are just as likely to cause these adverse effects.

5-**Caution** should be exercised when ARBs are used **in patients with angioedema from ACE inhibitors because crossreactivity** has been reported. Similar to ACE inhibitors, ARBs are contraindicated in pregnancy.

D-Angiotensin Receptor–Neprilysin Inhibitor (ARNI)

1-Valsartan/Sacubitril is an ARNI approved for HF. In patients with HFrEF (**Further reading 1)**, the use of ARNi is recommended to reduce morbidity and mortality [(2)].

2-**Neprilysin is an enzyme that degrades bradykinin** and **other endogenous vasodilator and natriuretic peptides**. By reducing neprilysin-mediated breakdown of these compounds, vasodilation, diuresis, and natriuresis are enhanced, and renin and aldosterone secretion is inhibited.

3-**In patients with HFrEF, ARNI is preferred over either ACE inhibitors or ARBs t**o **improve survival**. Patients receiving ACE inhibitors or ARBs can be switched to ARNI or ARNI can be used as initial treatment in patients with newly detected HFrEF.

4-**Discontinue ACE inhibitors 36 hours prior to initiating the ARNI**; no waiting period is needed in patients receiving an ARB.

5-**Closely monitor** BP, serum potassium, and renal function after the start of therapy and after each titration step.

6-**The most common adverse effects include** hypotension, dizziness, hyperkalemia, worsening renal function, and cough. **Angioedema is most common with sacubitril/valsartan than with enalapril.**

7-Sacubitril/valsartan is **contraindicated in patients with a history of angioedema associated with an ACE inhibitor or ARB.** It is also **contraindicated in pregnancy** and should **not be used concurrently with ACE inhibitors or other ARBs**.

E-β-Blockers

1-β-Blockers antagonize the effects of the sympathetic nervous systems in HF and slow disease progression. β-**blockers reduce HF mortality, and hospitalizations**.

2-The ACC/AHA guidelines recommend use of β-blockers in **all stable patients** with HFrEF in the absence of contraindications or a clear history of β-blocker intolerance.

3-Patients should receive a β-blocker **even if symptoms are mild or well controlled** with other GDMT.

4-**Carvedilol**, **metoprolol succinate** (CR/XL), and **bisoprolol** are the only β-blockers shown to reduce mortality in large HF trials.

5-Initiate β-blockers in **stable patients who have no or minimal evidence of fluid overload**. **Because of their negative inotropic effects**, start β-blockers in very low doses with slow upward dose titration to avoid symptomatic worsening.

6-**Inform patients that HF symptoms may actually worsen during the initiation period**.

7-**Adverse effects include** bradycardia or heart block, hypotension, fatigue, impaired glycemic control in diabetic patients, bronchospasm in patients with asthma, and worsening HF.

F-Aldosterone Antagonists

1-**Spironolactone** and **eplerenone** block mineralocorticoid receptors, the target for aldosterone.

2-Current guidelines recommend **adding a low-dose aldosterone antagonist** to standard therapy (**Further reading 2)** provided that serum potassium and renal function can be carefully monitored.

3-**Start with low doses**. Avoid aldosterone antagonists in patients with renal impairment, elevated serum potassium, or history of severe hyperkalemia.

4-Spironolactone also interacts with androgen and progesterone receptors, which may lead to **gynecomastia**, **impotence**, and **menstrual irregularities** in some patients.

G-Sodium Glucose Cotransporter Type 2 (SGLT2) Inhibitors

1-SLGT2 inhibitors **inhibit glucose and sodium reabsorption** in the proximal kidney tubules, which leads to **osmotic diuresis and natriuresis**, and **reduction in arterial pressure**

2-In patients with **symptomatic chronic HFrEF**, SGLT2i (**Dapagliflozin** or **empagliflozin**) are recommended to reduce **morbidity** and **mortality**, irrespective of the presence of type 2 diabetes (**with or without diabetes**) [(2)].

3-Patients should be advised to **avoid abrupt changes in position** as orthostasis may occur in the setting of overdiuresis.

H-Nitrates and Hydralazine

1-Isosorbide dinitrate (**ISDN**) is a venodilator that **reduces preload**, whereas **hydralazine** is a direct arterial vasodilator that **reduces systemic vascular resistance** (SVR) and increases stroke volume and CO.

2-Guidelines recommend **addition of hydralazine/ISDN** to **black patients** with HFrEF (**Further reading 3) who are receiving optimal medical therapy** [(2)].

3-The combination can also be useful in patients **unable to tolerate** either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or hypotension.

I-Ivabradine

1-Ivabradine inhibits the **If current** in the sinoatrial node that is responsible for controlling HR, thereby slowing the HR. It does not affect AV conduction, BP, or myocardial contractility.

2-Because of the clear benefits of β-blockers on mortality, clinicians should titrate to the maximum tolerated doses before considering use of Ivabradine (Patients are either on a maximally tolerated dose of a β-blocker or have a contraindication to β-blocker use).

J-Digoxin

1-Studies of digoxin in HF showed either neutral effects or reductions in hospitalizations and either neutral or detrimental effects of digoxin on mortality.

2-So digoxin is **not considered a first-line agent in HF.** In patients with **symptomatic HFrEF despite GDMT** (or who are unable to tolerate GDMT), digoxin might be considered to **improve symptoms and reduce hospitalizations** [(2)].

3-Digoxin may also be considered to **help control ventricular rate** in patients with HFrEF and supraventricular arrhythmias.

K-Vericiguat

1-Vericiguat modulates endothelial dysfunction; **it is a soluble guanylate cyclase activator (sGC) t**hat **enhances the effect of nitric oxide** (NO) and regulate contractility and diastolic function.

2-In a clinical trial, patients with HFrEF receiving vericiguat demonstrated **a significant, but modest, reduction in cardiovascular death or HF hospitalization.**

3-The drug was well tolerated overall, but there was an unexplained **greater incidence of anemia** in patients treated with vericiguat.

4-Vericiguat may be considered **in addition to optimized HF therapy** to **reduce morbidity and mortality** in patients at high risk **with worsening HFrEF** [(2)]**.**

5-It is not indicated in HFpEF due to lack of benefit and safety data.

Pharmacologic Therapy for HFpEF

1-**SGLT2i** should be initiated **in all individuals with HFpEF** lacking contraindications [3].

2-**Diuretics** should be used for symptom relief **in volume overload** [4].

3-The addition of **aldosterone antagonists, ARNIs or ARBs may be considered** (**further reading 4**) [3].

Reference

1-Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.
2-Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 Apr 1;145(18).
3-Kittleson MM, Gurusher Panjrath, Kaushik Amancherla, Davis LL, Deswal A, Dixon DL, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure with Preserved Ejection Fraction. Journal of the American College of Cardiology. 2023 Apr 1;81(18).
4-ACCP 2023.

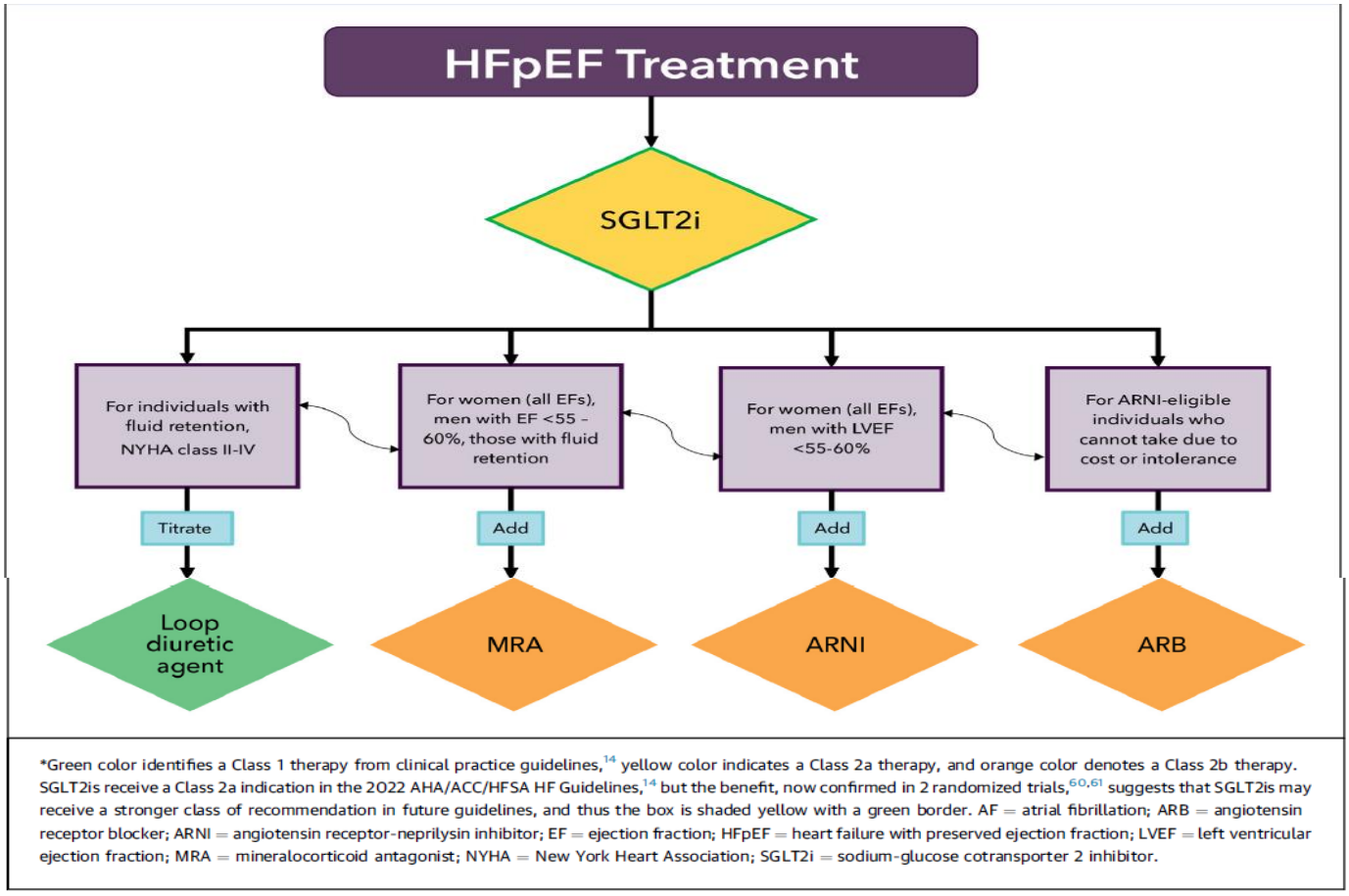
Further reading

1-And NYHA class II to III symptoms [2].

2- in (NYHA class II–IV [2]) patients.

3- (NYHA class III or IV) [2].

4-Treatment Algorithm for Guideline-Directed Medical Therapy in HFpEF [3].



*Green color identifies a Class 1 therapy from clinical practice guidelines,[14] yellow color indicates a Class 2a therapy, and orange color denotes a Class 2b therapy. SGLT2is receive a Class 2a indication in the 2022 AHA/ACC/HFSA HF Guidelines,[14] but the benefit, now confirmed in 2 randomized trials,[60,61] suggests that SGLT2is may receive a stronger class of recommendation in future guidelines, and thus the box is shaded yellow with a green border. AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.