**College of Pharmacy**

**Fourth year. Clinical Pharmacy**

**Cardiovascular disorders**

**Heart Failure**

**Introduction**

1-Heart failure (HF) is a progressive syndrome that can result from any changes in cardiac structure or function **that impair the ability of the ventricle to fill with or eject blood**.

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-Preserved LV systolic function (ie, normal LVEF) with diastolic dysfunction 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) Tac**h**ycardia 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** [angiotensin II, norepinephrine, aldosterone, natriuretic peptides, arginine vasopressin (AVP)] 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.**

**8-Common precipitating factors** that may cause a previously compensated HF patient to decompensate include myocardial ischemia and MI, pulmonary infections, nonadherence with diet or drug therapy, and inappropriate medication use.

9-Dr**ugs may precipitate or exacerbate HF** through negative inotropic effects, direct cardiotoxicity, or increased sodium and water retention.

**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-A complete **history and physical examination** with appropriate laboratory testing are essential in evaluating patients with suspected HF.

2-**Laboratory tests for identifying disorders that may cause or worsen HF include** renal, hepatic, thyroid function tests, and iron studies; lipid profile; and A1C.

3-**Serum creatinine** may be increased due to hypoperfusion; preexisting renal dysfunction can contribute to volume overload. B-type natriuretic peptide (BNP) and NT-proBNP are increased.

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

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

6-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.

7-The American College of Cardiology/American Heart Association (ACC/AHA) staging system provides (**Stages A, B, C, and D**) a more comprehensive framework for (evaluating, preventing, and treating HF).

**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**

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

**ACC/AHA Stage A:**

1-These are patients **at high risk for developing HF**. **Identify and modify risk factors** to prevent development of structural heart disease and subsequent HF.

2-Although treatment must be individualized, **ACE inhibitors or ARBs are recommended for HF prevention in patients with multiple vascular risk factors.**

**ACC/AHA Stage B:**

1-These patients **have structural heart disease but no HF signs or symptoms**.

2-Patients with reduced LVEF (<40%) should receive an **ACE inhibitor (or ARB) and β-blocker** to prevent development of HF. Patients with a previous **MI** should also receive **a statin.**

**ACC/AHA Stage C:**

1-These patients have structural heart disease and **previous or current HF symptoms**.

2-Patients with HFrEF in stage C should receive an ACE inhibitor, ARB, or **angiotensin receptor–neprilysin inhibitor** (ARNI; valsartan–sacubitril) together with an β-blocker, **and an aldosterone antagonist** in eligible patients to reduce morbidity and mortality.

3-**Loop diuretics, hydralazine–isosorbide dinitrate (ISDN), digoxin, and ivabradine are also used in select patients.**

**ACC/AHA Stage D HFrEF:**

1-These patients **have persistent HF symptoms despite maximally tolerated GDMT**.

2-They should be considered for **specialized interventions**, including **mechanical** circulatory support, **continuous IV positive inotropic** therapy, cardiac **transplantation**, or hospice care (when **no additional treatments are appropriate**).

**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**, plus an **aldosterone antagonist in select patients**.

2-Administer a **diuretic if there is evidence of fluid retention**. A **hydralazine–nitrate combination, ivabradine, 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-Current guidelines recommend that **all patients with HFrEF**, regardless of whether or not symptoms are present, s**hould receive an ACE inhibitor to reduce morbidity and mortality**, unless there are contraindications.

3-Start therapy **with low doses** followed by gradual titration as tolerated to the target or maximally tolerated doses. Dose titration is usually accomplished by doubling the dose every 2 weeks.

4-**Evaluate blood pressure** (BP), renal function, and serum potassium at baseline and within 1–2 weeks after the start of therapy and after each dose increase.

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

6-**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.

7-Because cough is a bradykinin-mediated effect, replacement with an ARB is reasonable; however, caution is required because crossreactivity has been reported.

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

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

**C-Angiotensin Receptor Blockers**

1-Because ARBs do not affect bradykinin, **they are not associated with cough and have a lower risk of angioedema than ACE inhibitors.**

2-ARBs are now recommended **as an alternative** in patients who are unable to tolerate an ACE inhibitor due to cough or angioedema.

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-As with ACE inhibitors, initiate therapy **with low doses** and then titrate to target doses. **Evaluate** BP, renal function, and serum potassium within 1–2 weeks after starting therapy and after dosage increases.

5-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.

6-**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 to reduce the risk of cardiovascular death and hospitalization for HF in patients with NYHA **class II–IV HF** and **reduced LVEF.**

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 and NYHA class II–III symptoms tolerating an ACE inhibitor or ARB, **current guidelines recommend replacing those drugs with the ARNI to further reduce morbidity and mortality**.

4-**Discontinue ACE inhibitors 36 hours prior to initiating the ARNI**; no waiting period is needed in patients receiving an ARB. Titrate the initial starting dose to the target dose after 2–4 weeks.

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 ACE inhibitor and diuretic therapy.

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 or acute decompensation. Doses should be doubled no more often than every 2 weeks, as tolerated, until the target or maximally tolerated dose is reached.

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.

8-**Absolute contraindications include** uncontrolled bronchospastic disease, symptomatic bradycardia, advanced heart block without a pacemaker, and acute decompensated HF. However, β-blockers may be tried with caution in patients with asymptomatic bradycardia, COPD, or well-controlled asthma.

**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 to improve symptoms, reduce the risk of HF hospitalization, and i**ncrease survival in select patients** provided that serum potassium and renal function can be carefully monitored.

3-**Low-dose aldosterone antagonists may be appropriate for:**

(**A**) patients with mild to moderately severe HFrEF (NYHA class II–IV) who are receiving standard therapy, and (**B**) those with LV dysfunction and either acute HF or diabetes early after MI.

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

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

**G-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 **African Americans** with HFrEF and NYHA class III–IV symptoms treated with ACE inhibitors (or ARBs) and β-blockers.

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.

**H-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.

3-**Ivabradine is indicated to reduce the risk of hospitalization for worsening HF in patients** with LVEF ≤35% and are either on a maximally tolerated dose of a β-blocker or have a contraindication to β-blocker use.

4-The most **common adverse effects** are bradycardia, atrial fibrillation, and visual disturbances.

**I-Digoxin**

1-Although digoxin has positive inotropic effects, its benefits in HF are related to its neurohormonal effects. It attenuates the excessive sympathetic nervous system activation in HF and increases parasympathetic activity, thereby decreasing HR and enhancing diastolic filling.

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

3-So digoxin is **not considered a first-line agent in HF,** but a trial may be considered in conjunction with ACE inhibitors (or ARBs), β-blockers, and diuretics in patients with symptomatic HFrEF **to improve symptoms and reduce hospitalizations**.

4-Digoxin may also be considered to **help control ventricular rate** in patients with HFrEF and supraventricular arrhythmias, although β-blockers are generally more effective rate control agents, especially during exercise.

**Pharmacologic Therapy for HFpEF**

1-Many of the drugs are the same as those used to treat HFrEF (eg, diuretics, β-blockers), but the rationale and dosing may be different.

2-**A loop or a thiazide diuretic should be considered for patients with volume overload**. Use a loop diuretic for more severe volume overload or inadequate response to a thiazide.

3-**ACE inhibitors may be considered in all patients**, especially patients with symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor.

4-**ARBs may be considered in all patients**, especially those who are intolerant of ACE inhibitors.

5-**Aldosterone antagonists** can reduce the risk of hospitalization in patients who do not have contraindications and are not at risk for hyperkalemia. They may be beneficial for patients with elevated BNP or NT-proBNP.

6-β**-Blockers should be considered in patients with one or more of the following conditions**: (**1**) MI, (**2**) hypertension, and (**3**) atrial fibrillation requiring ventricular rate control.

7-**Nondihydropyridine** calcium channel blockers (CCB; **diltiazem** or **verapamil**) should be considered for patients **with atrial fibrillation** warranting ventricular rate control who either **are intolerant to or have not responded to a β-blocker**.

8-A **nondihydropyridine** or **dihydropyridine** (eg, **amlodipine**) CCB can be considered for **symptom-limiting angina or hypertension**.

**Reference**

**Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach,**

**11th Edition. 2021.**