HEART FAILURE

BY

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Definition of Heart Failure

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

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

- Preserved LV systolic function (ie, normal LVEF) with presumed diastolic dysfunction is termed **HF with preserved ejection fraction (HFpEF).**

Pathophysiology

- **Causes of systolic dysfunction** (decreased contractility)

- include reduced muscle mass

- (eg, myocardial infarction [MI]),
- dilated cardiomyopathies,
- ventricular hypertrophy.
- Ventricular hypertrophy can be caused by pressure overload (eg, systemic or pulmonary hypertension and aortic or pulmonic valve stenosis) or volume overload (eg, valvular regurgitation).

- **Causes of diastolic dysfunction** (restriction in ventricular filling)

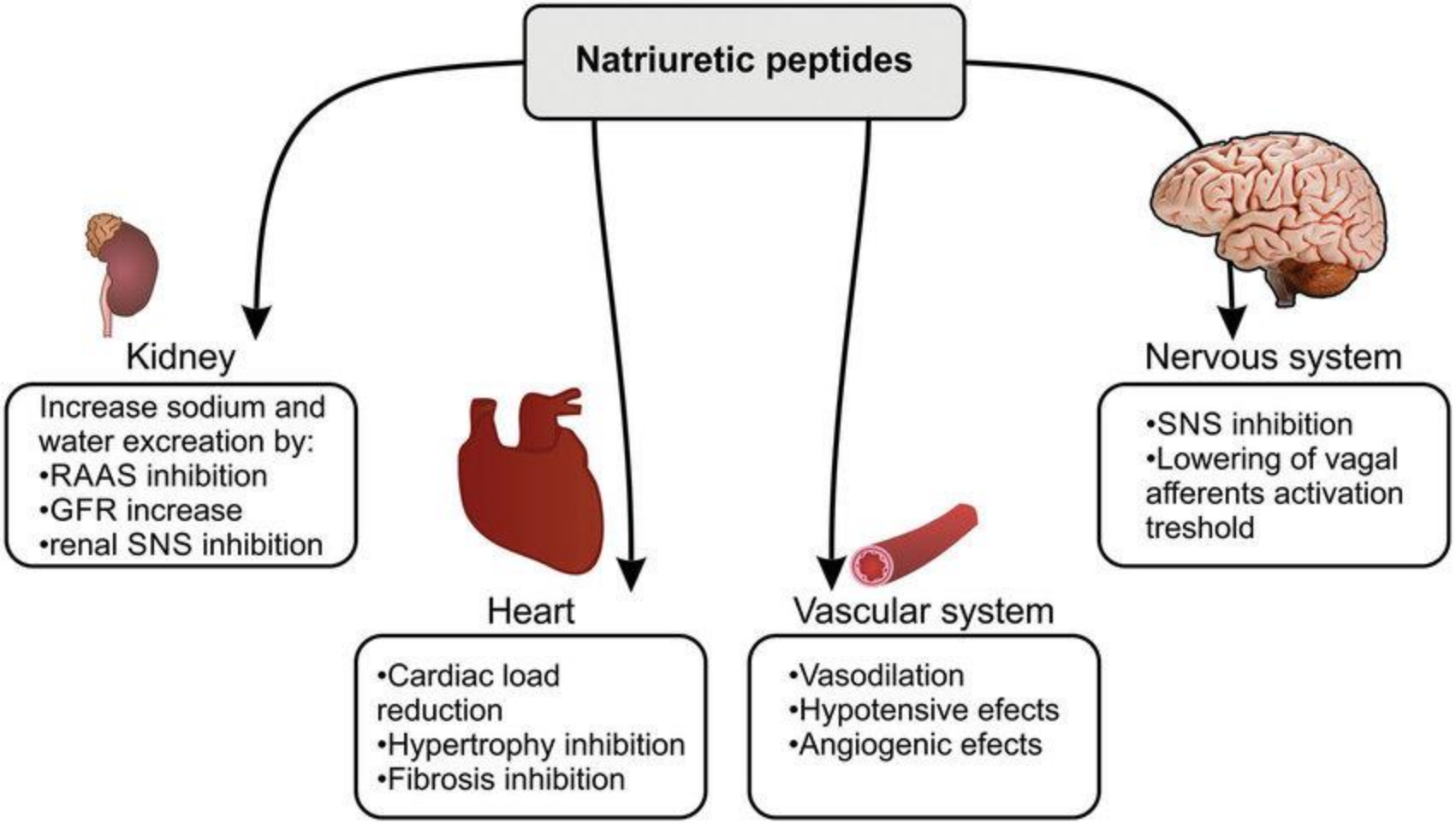
- include increased ventricular stiffness
- ventricular hypertrophy
- infiltrative myocardial diseases
- myocardial ischemia and MI
- mitral or tricuspid valve stenosis
- pericardial disease (eg, pericarditis and pericardial tamponade).

- 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) The Frank–Starling mechanism, whereby increased preload (through **sodium and water retention**) increases **stroke volume**
- (C) **vasoconstriction**
- (D) **ventricular hypertrophy and remodeling**.

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

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

Action of natriuretic peptide



- The alterations in ventricular function result **in further deterioration in cardiac systolic and diastolic functions** that further promotes the remodeling process.

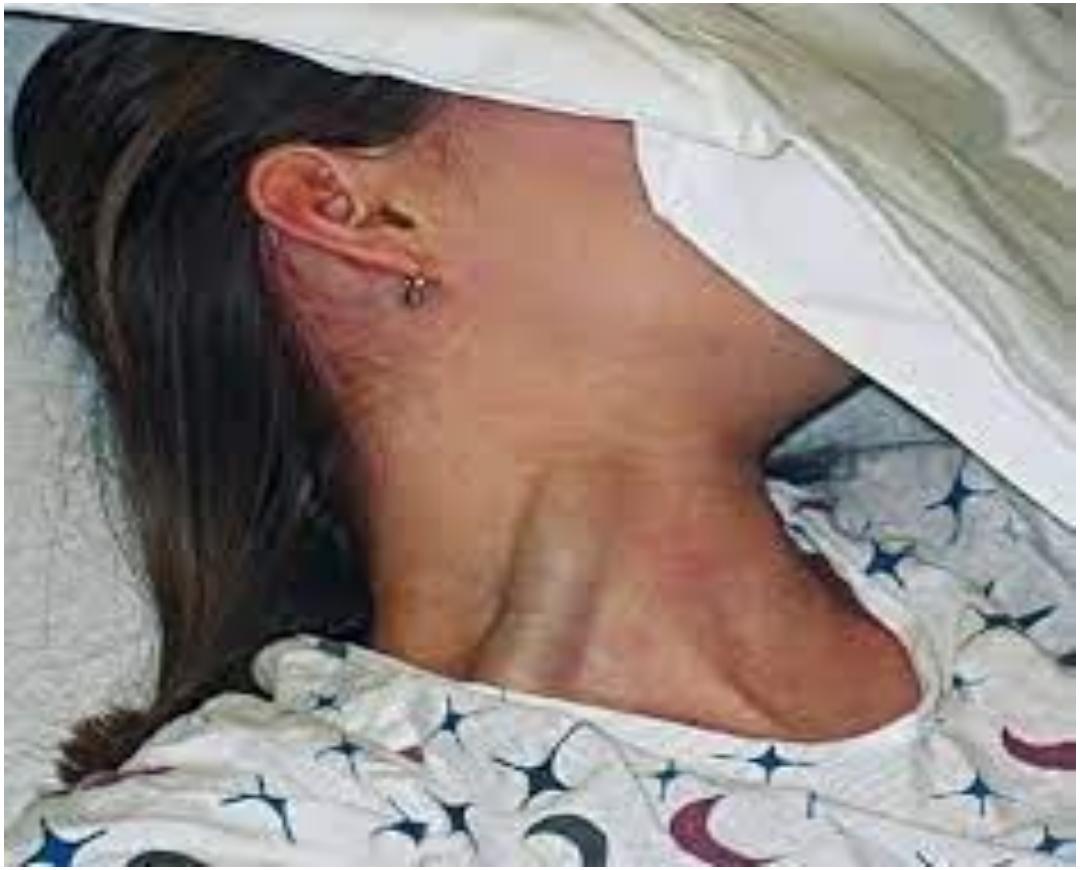
- **Common precipitating factors** that may cause a previously compensated HF patient to decompensate include myocardial ischemia and MI, pulmonary infections, nonadherence with diet or drug therapy, and inappropriate medication use.

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

Clinical presentation

- Patient presentation may range from asymptomatic to cardiogenic shock.
- **Primary symptoms are** dyspnea (especially on exertion) and fatigue, which lead to exercise intolerance.
- **Other pulmonary symptoms include:** orthopnea, paroxysmal nocturnal dyspnea (PND), tachypnea, and cough. Fluid overload can result in pulmonary congestion and peripheral edema.
- **Nonspecific symptoms may include** fatigue, nocturia, hemoptysis, abdominal pain, anorexia, nausea, bloating, ascites, poor appetite or early satiety, and weight gain or loss.
- **Physical examination may reveal** pulmonary crackles, cool extremities, tachycardia, narrow pulse pressure, cardiomegaly, symptoms of pulmonary edema (extreme breathlessness and anxiety, sometimes with coughing and pink, frothy sputum), peripheral edema, jugular venous distention (JVD), hepatomegaly, and mental status changes

jugular venous distention (JVD



Diagnosis

- 1-A complete **history and physical examination**
- 2-**Laboratory tests for identifying disorders that may cause or worsen HF include** complete blood cell count; serum electrolytes (including calcium and magnesium); renal, hepatic, thyroid function tests, and iron studies; urinalysis; lipid profile; and A1C. Hyponatremia may indicate worsening volume overload and/or disease progression and is associated with reduced survival.
- 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 identify abnormalities of the pericardium, myocardium, or heart valves and quantify LVEF to determine if systolic or diastolic dysfunction is present.

The New York Heart Association Functional **Classification System(NYHA)**

-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.

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).

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-Strategies include smoking cessation and control of hypertension, diabetes mellitus, and dyslipidemia.
- 3-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**. Treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process.
- 2-In **addition to treatment measures outlined for stage A**, patients with reduced LVEF (<40%) should receive an **ACE inhibitor (or ARB) and β-blocker** to prevent development of HF, regardless of whether they have had an MI.
- 3-Patients with a previous **MI and reduced LVEF** should also receive an ACE inhibitor or ARB, β-blockers, **and a statin.**

ACC/AHA Stage C:

- 1-These patients have structural heart disease and **previous or current HF symptoms** and include both HFrEF and HFpEF.
- 2-In addition to treatments for stages A and B, patients with HFrEF in stage C should receive guideline-directed medical therapy (GDMT) that includes 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

- 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**.
- 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

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

- diuretics **do not alter disease progression or prolong survival**

- - diuretics are not required for patients without fluid retention.

- **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.
- **Thiazides** may be pre**f**erred over loop diuretics in patients with only **mild fluid retention and elevated BP** because of their more persistent antihypertensive effects.
- **Loop diuretics** (furosemide, bumetanide, and torsemide) are **usually necessary** to restore and maintain euvolemia in HF.
- Unlike thiazides, loop diuretics **maintain their effectiveness in the presence of impaired renal function**, although higher doses may be necessary.

B-Angiotensin-Converting Enzyme Inhibitors

- ACE inhibitors improve symptoms, slow disease progression, **and decrease mortality** in patients with HFrEF.
- 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**,
- The benefits of ACE inhibitors are independent of HF etiology (ischemic vs nonischemic) and are greatest in patients with the most severe symptoms.
- 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.
- **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.

- Although symptoms may improve within a few days of starting therapy, **it may take weeks to months before the full benefits are apparent**. Even if symptoms do not improve, continue long-term therapy to reduce mortality and hospitalizations.
- **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.
- Because cough is a bradykinin-mediated effect, replacement with an ARB is reasonable; however, caution is required because crossreactivity has been reported.
- **Angioedema** occurs in approximately 1% of patients and **is potentially life threatening**; ACE inhibitors are contraindicated in patients with a history of angioedema.

C-Angiotensin Receptor Blockers

- ARBs are now recommended **as an alternative** in patients who are unable to tolerate an ACE inhibitor due to cough or angioedema
- Although numerous ARBs are available, **only candesartan, valsartan, and losartan** are **recommended in the guidelines** because efficacy has been demonstrated in clinical trials.
- 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

- 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.
- **Careful monitoring** is required when an ARB is used with another inhibitor of the renin-angiotensin aldosterone (RAAS) system (eg, ACE inhibitor or aldosterone antagonist) because this combination increases the risk of these adverse effects.

D-Angiotensin Receptor–Neprilysin Inhibitor (ARNI)

- **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.**
- Neprilysin is an enzyme that degrades bradykinin and other endogenous vasodilator and natriuretic peptides.
- vasodilation, diuresis, and natriuresis are enhanced, and renin and aldosterone secretion is inhibited.
- 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.
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- 5-**Closely monitor** BP, serum potassium, and renal function after the start of therapy and after each titration step.
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- 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.**
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- 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

- β-Blockers antagonize the effects of the sympathetic nervous systems in HF and slow disease progression. β**-blockers reduce HF mortality, and hospitalizations**.
- 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.
- Patients should receive a β-blocker **even if symptoms are mild or well controlled** with ACE inhibitor and diuretic therapy.

- β-Blockers are also recommended for asymptomatic persons with a reduced LVEF (stage B) to decrease the risk of progression to HF.
- **Carvedilol**, **metoprolol succinate** , and **bisoprolol** are the only β-blockers shown to reduce mortality in large HF trials.
- 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.

- **Inform patients that** β-blocker therapy is expected to positively influence disease progression and survival **even if there is little symptomatic improvement**. In addition, **dose titration is a long**, **gradual process**; **response to therapy may be delayed**; and **HF symptoms may actually worsen during the initiation period**.
- **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. [In the **kidney**, inhibit sodium reabsorption and potassium excretion, In the **heart**, attenuating cardiac fibrosis and ventricular remodeling]. Aldosterone antagonists also attenuate the proinflammatory state, atherogenesis, and oxidative stress caused by 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) (**B**) those with LV dysfunction and either acute HF or diabetes early after MI.

- Start with low doses. Avoid aldosterone antagonists in patients with renal impairment, elevated serum potassium, or history of severe hyperkalemia.
- 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.
- 4-**Obstacles to successful therapy with the combination include** the need for frequent dosing (ie, three times daily with the fixed-dose combination product), high frequency of adverse effects (eg, headache, dizziness, and GI distress), and increased cost for the fixed-dose combination product.

H-Ivabradine

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- 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% who are in sinus rhythm with resting HR ≥70 bpm 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(harmful) 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 GDMT including 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.
- 5-In the absence of digoxin toxicity or serious adverse effects, digoxin should be continued in most patients. Digoxin withdrawal may be considered for asymptomatic patients who have significant improvement in systolic function with optimal ACE inhibitor and β-blocker treatment.

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-Avoid lowering preload excessively, which may reduce stroke volume and CO. Start diuretics at low doses to avoid hypotension and fatigue
- 4-**ACE inhibitors may be considered in all patients**, especially patients with symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor.

- 5-**ARBs may be considered in all patients**, especially those who are intolerant of ACE inhibitors.
- 6-**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.
- 7-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.
- 8-**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**.
- 9-A **nondihydropyridine** or **dihydropyridine** (eg, **amlodipine**) CCB can be considered for **symptom-limiting angina or hypertension**.

Treatment of acute decompensated heart failure (ADHF)

- **Acute decompensated heart failure** involves patients with **new or worsening signs or symptoms** (often resulting from volume overload and/or low CO) **requiring medical intervention**, such as emergency department visit or hospitalization.

Goals of Treatment:

- improve hemodynamic stability
- and reduce short-term mortality so the patient can be discharged in a stable compensated state on oral drug therapy.
- Admission to an **intensive care unit** (ICU) may be required if the patient experiences hemodynamic instability requiring frequent monitoring of vital signs, invasive hemodynamic monitoring, or rapid titration of IV medications with close monitoring.

- **Symptoms of volume overload** include dyspnea, orthopnea, PND, ascites, GI symptoms (poor appetite, nausea, early satiety), peripheral edema, and weight gain. **Signs of volume overload include** pulmonary crackles, elevated jugular venous pressure, HJR, and peripheral edema.
- **Low output symptoms** include altered mental status, fatigue, GI symptoms (similar to volume overload), and decreased urine output. **Low output signs** include tachycardia, hypotension (more commonly) or hypertension, cool extremities, pallor, and cachexia.

- **Laboratory testing may include** BNP or NT-proBNP, thyroid function tests, complete blood count, cardiac enzymes, and routine serum chemistries (eg, serum creatinine, liver function tests).

- Ascertain hemodynamic status to guide initial therapy. Patients may be categorized into one of
- **four hemodynamic subsets** based on

- volume status (**euvolemic** or “dry” vs **volume overloaded** or “wet”)

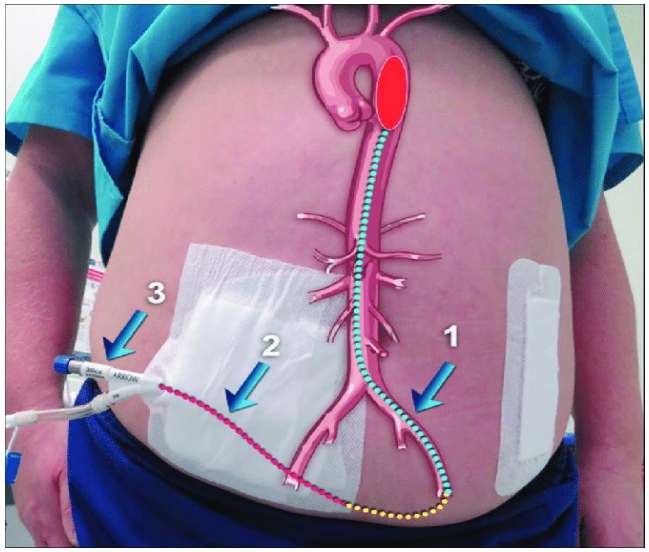
- **CO** (**adequate** CO or “warm” vs **hypoperfusion** or “cold”).
- **If fluid retention** is evident on physical exam, **start aggressive diuresis**, preferably with IV diuretics

- In the absence of cardiogenic shock or symptomatic hypotension, strive to continue all GDMT for HF. **β-blockers may be temporarily held or dose reduced** if recent changes are responsible for acute decompensation.
- Other GDMT **(ACE inhibitors, ARBs, ARNI, and aldosterone antagonists) may also need to be temporarily withheld in the presence of renal dysfunction**, with close monitoring of serum potassium.
- Place all patients with congestive symptoms **on sodium restriction** (<2 g daily) and consider fluid restriction for refractory symptoms

- 12-Consider **noninvasive ventilation** for patients in respiratory distress due to acute pulmonary edema.
- 13-**Provide pharmacologic thromboprophylaxis** with unfractionated heparin or low-molecular-weight heparin for most patients with limited mobility; **consider mechanical thromboprophylaxis** with intermittent pneumatic compression devices in patients at high risk for bleeding.
- Most nonpharmacologic therapies for ADHF are reserved for patients failing pharmacologic therapy. **Ultrafiltration and wireless invasive hemodynamic monitoring** (W-IHM) may be used to manage congestive symptoms.

- Temporary **mechanical circulatory support** (MCS) with an **intraaortic balloon pump** (IABP), **ventricular assist device** (VAD), or **extracorporeal membrane oxygenation** (ECMO) may be considered for hemodynamic stabilization until the underlying etiology has been corrected or until definitive therapy (eg, cardiac transplantation). Systemic anticoagulant therapy is generally required to prevent device thrombosis, regardless of the method selected.
- **Cardiac transplantation** is the best option for patients with irreversible advanced HF. New surgical strategies such **myocardial cell transplantation** offer additional options for patients ineligible for device implantation or heart transplantation

- IABP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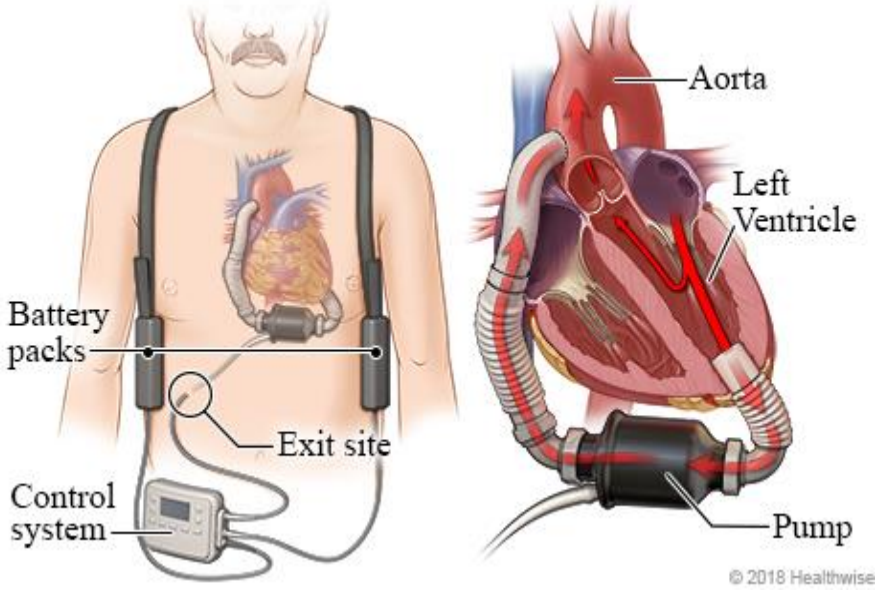
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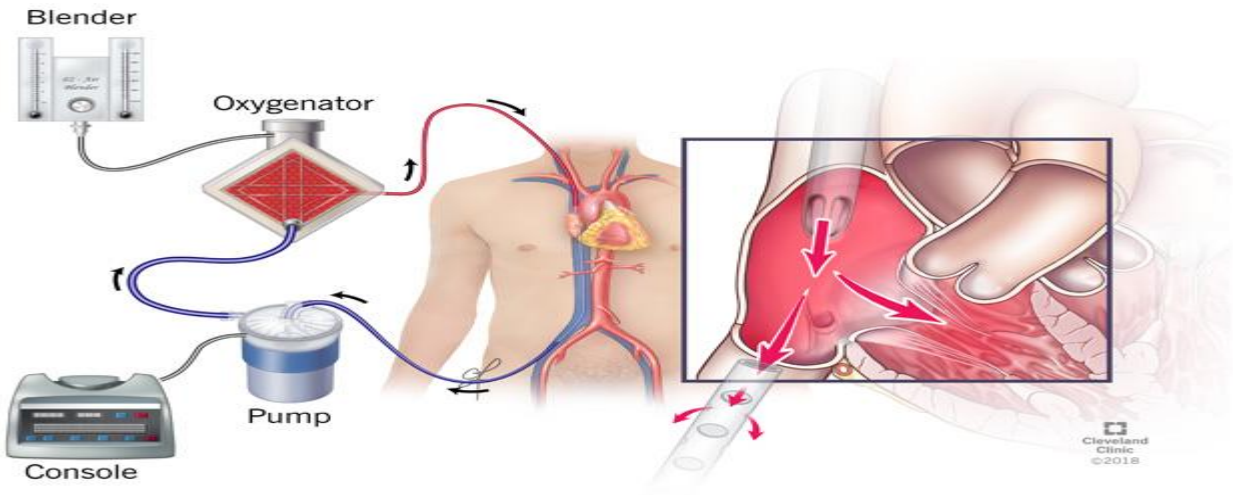
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Pharmacologic Therapy for ADHF

- **A-Loop Diuretics**
- Current guidelines **recommend IV loop diuretics** (furosemide, bumetanide) as first-line therapy for **ADHF patients with volume overload**.
- Bolus administration **reduces preload** by functional **venodilation** within 5–15 minutes and **later** (>20 minutes) **via sodium and water excretion**, thereby improving pulmonary congestion.
- **Diuretic resistance may be improved by** administering larger IV **bolus** doses, transitioning from IV bolus to continuous IV **infusions**, or **adding a second diuretic** with a different mechanism of action, such as a distal tubule blocker (eg, oral metolazone, oral hydrochlorothiazide, or IV chlorothiazide). In the outpatient setting, a very low dose of the thiazide-type diuretic or infrequent administration (eg, 1–3 times weekly) is recommended.

B-Vasopressin Antagonists

- Vasopressin receptor antagonists affect one or two AVP (**antidiuretic hormone**) receptors, V1A or V2. Stimulation of V1A receptors (located in vascular smooth muscle cells and myocardium) results in vasoconstriction, myocyte hypertrophy, coronary vasoconstriction, and positive inotropic effects. V2 receptors are located in renal tubules, where they regulate water reabsorption.
- **Tolvaptan** selectively binds to and inhibits the V2 receptor. It is an oral agent indicated for hypervolemic and euvolemic **hyponatremia in patients with HF**. The most common **side effects** are dry mouth, thirst, urinary frequency, constipation, and hyperglycemia.
- **Conivaptan** nonselectively inhibits both the V1A and V2 receptors. It is an IV agent indicated for hypervolemic and euvolemic hyponatremia due to a variety of causes but is not indicated for patients with HF.

- 2-**Monitor patients** closely to avoid an **excessively rapid rise in serum sodium** requiring drug discontinuation.
- 3-**The role of vasopressin receptor antagonists in the long-term management of HF is unclear**. **Results of studies do not support routine use of tolvaptan in ADHF** (e.g, causes worsening renal function, and failed to demonstrate improved long-term outcomes, including morbidity and mortality), and it **should be reserved for managing severe hyponatremia.**

C-Vasodilators

- 1-**Venodilators reduce preload** by increasing venous capacitance, and improve symptoms of pulmonary congestion. **Arterial vasodilators** counteract (the peripheral vasoconstriction and impaired CO) so, **decreasing afterload and causing increased CO**. **Mixed vasodilators** act on both arterial resistance and venous capacitance vessels, **reducing congestive symptoms while increasing CO.**
- IV **vasodilators should be considered before positive inotropic** therapy in patients with low CO and elevated SVR. However, **hypotension may preclude their use in patients with preexisting low BP or SVR.**
- 3-**IV nitroglycerin is often preferred for preload reduction in ADHF**, especially in patients with pulmonary congestion. In higher doses, nitroglycerin displays potent coronary vasodilating properties and beneficial effects on myocardial oxygen demand and supply, making it the vasodilator of choice for patients with severe HF and ischemic heart disease.

- **Hypotension** and **excessive decrease in pulmonary capillary wedge pressure (PCWP) are important dose-limiting side effects**. **Tolerance** to the hemodynamic effects may develop over 12–72 hours of continuous administration.
- 6-**Sodium nitroprusside** is a **mixed arteriovenous vasodilator**. **Hypotension** is an important dose-limiting adverse effect of nitroprusside, and its use should be primarily reserved **for patients with elevated SVR**.
- Nitroprusside is effective in the short-term management of severe HF in a variety of settings (eg, acute MI, valvular regurgitation, after coronary bypass surgery, and ADHF).

- **Nitroprusside-induced cyanide and thiocyanate toxicity** are unlikely when doses <3 mcg/kg/min are administered for less than 3 days, except in patients with significant renal impairment (ie, serum creatinine >3 mg/dL [265 µmol/L]).

D-Inotropes

- 1-Prompt correction of low CO in patients with “cold” subsets (III and IV) is required to **restore peripheral tissue perfusion and preserve end-organ function**.
- Although IV inotropes can improve hypoperfusion by enhancing cardiac contractility, potential adverse outcomes limit their use to select patients with refractory ADHF.
- **Inotropes should be considered only as a temporizing measure to maintain end-organ perfusion** in patients with cardiogenic shock or severely depressed CO and low systolic BP (ie, ineligible for IV vasodilators).
- **Dobutamine** and **milrinone** produce similar hemodynamic effects, but dobutamine usually causes more pronounced increases in HR, and **milrinone is associated with greater relaxation in arterial smooth muscle.**

- Dobutamine is a β1- and β2-receptor agonist with some α1-agonist effects; its positive inotropic effects are due to effects on β1-receptors.
- Cardiac Index (CI) is increased because of inotropic stimulation, arterial vasodilation, and a variable increase in HR. **It causes relatively little change in mean arterial pressure (MAP)**. Dobutamine should be considered over milrinone when a significant decrease in MAP might further compromise hemodynamic function.
- Dobutamine's major **adverse effects are tachycardia and ventricular arrhythmias**.

- Milrinone inhibits phosphodiesterase III and produces positive inotropic and arterial and venous vasodilating effects (an **inodilator**). It has supplanted use of amrinone, which has a higher rate of thrombocytopenia.
- Milrinone also lowers pulmonary PCWP by venodilation and **is particularly useful in patients with a low CI and elevated LV filling pressure**. Use milrinone cautiously in severely hypotensive HF patients because it does not increase, and may even decrease, arterial BP.
- The most notable adverse events of Milrinone are **arrhythmia, hypotension, and thrombocytopenia**. Measure the platelet count before and during therapy.

- **Norepinephrine** (stimulates α1- and β1-adrenergic receptors) and **dopamine** [endogenous precursor of norepinephrine that stimulates α1, β1, β2, and D1 (vascular dopaminergic) receptors) have combined inotropic and vasopressor activity.
- Although therapies that increase SVR are generally avoided in ADHF, they may be **required in select patients where marked hypotension precludes use of traditional inotropes** (eg, septic shock, refractory cardiogenic shock).

- Positive inotropic effects of dopamine mediated primarily by β1-receptors are prominent with **doses of 2–5 mcg/kg/min**. At doses between **5 and 10 mcg/kg/min, chronotropic** and α1-mediated vasoconstriction become more prominent and MAP usually increases.
- Studies of low-dose dopamine (2–5 mcg/kg/min) given with IV loop diuretics to enhance diuresis demonstrated no improvements. **Thus, low-dose dopamine may not provide any advantages over traditional inotropes in this setting**.