
Pharmacotherapy of Heart Failure

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Introduction

- *Heart failure (HF)*
 - *is a progressive clinical syndrome caused by inability of the heart to pump sufficient blood to meet the body's metabolic needs.*
- HF can result from any disorder that affects the ability of the heart to
 - contract (systolic dysfunction) and/or
 - relax (diastolic dysfunction).

Cont...

- 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) are
 - reduced muscle mass (eg, myocardial infarction [MI]),
 - dilated cardiomyopathies, and
 - 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, shunts, and high-output states).

Cont...

- **Causes of diastolic dysfunction** (restriction in ventricular filling) are:
 - increased ventricular stiffness,
 - ventricular hypertrophy,
 - infiltrative myocardial diseases,
 - myocardial ischemia and MI,
 - mitral or tricuspid valve stenosis, and
 - pericardial disease (eg, pericarditis and pericardial tamponade).
- The leading causes of HF are **coronary artery disease and hypertension**.

Cont...

- Regardless of the index event, decreased cardiac output results in **activation of compensatory responses** to maintain circulation:
 - (1) tachycardia and increased contractility through sympathetic nervous system activation;
 - (2) the Frank–Starling mechanism, whereby increased preload (through sodium and water retention) increases stroke volume;
 - (3) vasoconstriction; and
 - (4) ventricular hypertrophy and remodeling.

Cont...

- Although these **compensatory mechanisms** initially maintain cardiac function,
 - they are responsible for the symptoms of HF and
 - contribute to disease progression.
- In the *neurohormonal model of HF*,
 - *an initiating event (eg, acute MI) leads to* decreased cardiac output;
 - the HF state then becomes a systemic disease whose progression is mediated largely by neurohormones and autocrine/paracrine factors that drive
 - myocyte injury, oxidative stress, inflammation, and extracellular matrix remodeling.

Cont...

- **These substances include**
 - angiotensin II,
 - norepinephrine,
 - aldosterone,
 - natriuretic peptides, and
 - arginine vasopressin.

Cont...

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

Cont....

- **Drugs 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,
 - tachypnea, and
 - cough.

Cont...

- 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, mental status changes, and weight gain.

Cont...

- **Physical examination findings may include**
 - Pulmonary crackles,
 - S3 gallop,
 - Cool extremities,
 - Cheyne–Stokes respiration,
 - 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,
 - hepatojugular reflux, and
 - hepatomegaly.

DIAGNOSIS

- Consider diagnosis of HF in patients with **characteristic signs and symptoms.**
- **A complete history and physical examination** with appropriate **laboratory testing** are essential in evaluating patients with suspected HF.

Cont...

- **Laboratory tests** for identifying disorders that may cause or worsen HF include:
 - complete blood cell count;
 - serum electrolytes (including calcium and magnesium);
 - renal, hepatic, and thyroid function tests;
 - urinalysis;
 - lipid profile; and
 - A1C.
 - B-type natriuretic peptide (BNP) will generally be greater than 100 pg/mL.

Cont...

- **Ventricular hypertrophy** can be demonstrated on **chest radiograph** or **electrocardiogram (ECG)**.
- Chest radiograph may also show **pleural effusions** or **pulmonary edema**.
- **Echocardiogram** can identify:
 - abnormalities of the pericardium, myocardium, or heart valves and
 - quantify LVEF to determine if systolic or diastolic dysfunction is present.

Cont...

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

Functional Class	
I	patients have no limitation of physical activity,
II	patients have slight limitation,
III	patients have marked limitation
IV	patients are unable to carry on physical activity without discomfort.

Cont...

- The American College of Cardiology/American Heart Association (ACC/AHA) staging system **provides 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.
- Drugs that aggravate HF should be **discontinued if possible.**

Cont...

- **Non-pharmacologic interventions** include:
 - cardiac rehabilitation and
 - restriction of fluid intake (maximum 2 L/day from all sources) and
 - Restriction of dietary sodium (<2–3 g of sodium/day).

Cont...

- **ACC/AHA Stage A:** These are patients at high risk for developing heart failure.
 - The emphasis is on identifying and modifying risk factors to prevent development of structural heart disease and subsequent HF.
 - Strategies include **smoking cessation and control of hypertension, diabetes mellitus, and dyslipidemia.**
 - Although treatment must be individualized,
 - **angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)** are recommended for HF prevention in patients with multiple vascular risk factors.

Cont...

- **ACC/AHA Stage B:**

- **In these patients with structural heart disease but no HF signs** or symptoms, treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process.
- In addition to treatment measures outlined for stage A, patients with reduced LVEF should receive an ACE inhibitor (or ARB) and a β -blocker to prevent development of HF, regardless of whether they have had an MI.
- Patients with a previous MI and reduced LVEF should also receive an ACE inhibitor or ARB, evidence-based β -blockers, and a statin.

Cont...

- **ACC/AHA Stage C:**
 - **These patients have structural heart disease and previous or current HF symptoms and include both HFrEF and HFpEF.**
 - In addition to treatments for stages A and B, patients with HFrEF should be treated with guideline-directed medical therapy (GDMT) that includes an ACE inhibitor or ARB and an evidence based β -blocker
 - **Loop diuretics, aldosterone antagonists, and hydralazine–isosorbide dinitrate (ISDN)** are also used routinely.
 - Digoxin, ivabradine, and sacubitril/valsartan can be considered in select patients.

Cont...

- **Other general measures** include:
 - moderate sodium restriction,
 - daily weight measurement,
 - immunization against influenza and pneumococcus, modest physical activity, and
 - avoidance of medications that can exacerbate HF.

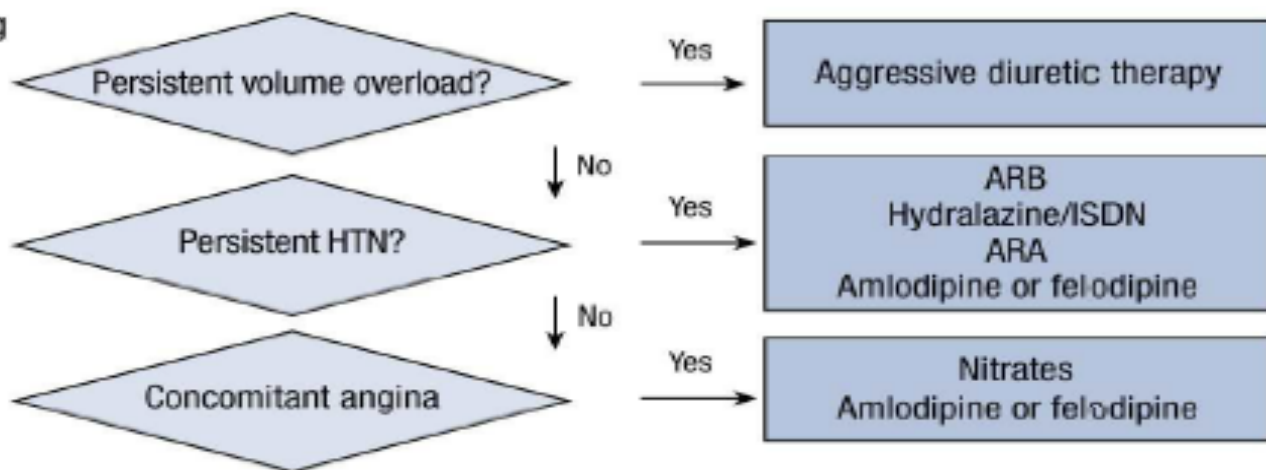
GDMT for HFrEF Stage C

Initiate and titrate ACEI or ARB and β -blocker^a (Class I, Evidence A)
Initiate loop diuretic if fluid retention (Class I, Evidence C)

↓ Add

ARA ^b	(Class I, Evidence A)
ARB	(Class IIa, Evidence A as alternative to ACEI) (Class IIb, Evidence B if persistently symptomatic on GDMT)
Digoxin ^c	(Class IIa, Evidence B if persistently symptomatic on GDMT)
Hydralazine/ISDN	(Class I, Evidence A if African American and persistently symptomatic on GDMT) (Class IIa, Evidence B if ACEI/ARB intolerant)
Sacubitril/valsartan ^d	(Alternative to ACEI or ARB if NYHA class II-IV symptoms)
Ivabradine ^d	(Sinus rhythm with heart rate >70 bpm)

Any time during therapy...



Cont...

- **ACC/AHA Stage D HFrEF:**
 - These are patients with persistent HF symptoms despite maximally tolerated GDMT.
 - 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).
 - Restriction of sodium and fluid intake may be beneficial.

Cont...

- High doses of diuretics, combination therapy with a loop and thiazide diuretic, or mechanical fluid removal methods such as ultra-filtration may be required.
- Patients may be less tolerant to ACE inhibitors and β -blockers, so low starting doses, slow upward dose titration, and close monitoring are essential.

Cont...

- **Management of HFpEF:**
 - **Treatment includes controlling heart rate (HR) and blood pressure (BP), alleviating causes of myocardial ischemia, reducing volume, and restoring and maintaining sinus rhythm in patients with atrial fibrillation.**
 - Many of the drugs are the same as those used to treat HFrEF (eg, β -blockers and diuretics), but the rationale and dosing may be different.
 - Calcium channel blockers (eg, diltiazem, amlodipine, and verapamil) may be useful in HFpEF but have little utility in treating HFrEF.

PHARMACOLOGIC THERAPY

Drug Therapies for Routine Use in Stage C HFrEF

DIURETICS

- Compensatory mechanisms in HF stimulate excessive sodium and water retention, often leading to systemic and pulmonary congestion.
- Consequently, diuretic therapy (in addition to sodium restriction) is recommended for all patients with clinical evidence of fluid retention.
- However, because they do not alter disease progression or prolong survival, diuretics are not required for patients without fluid retention.
- In patients with HFpEF, diuretic treatment should be initiated at low doses to avoid hypotension and fatigue.

Cont....

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

Cont....

- Loop diuretics (**furosemide, bumetanide, and torsemide**) are usually necessary to restore and maintain euvolemia in HF.
- In addition to acting in the thick ascending limb of the loop of Henle, they induce a prostaglandin-mediated increase in renal blood flow that contributes to their natriuretic effect.
- Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses may be necessary.

TABLE 9–1

Drug Dosing Table

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose
Loop Diuretics				
Furosemide	Lasix	20–40 mg once or twice daily	20–160 mg once or twice daily	Cl _{cr} 20–50 mL/min: 160 mg once or twice daily Cl _{cr} <20 mL/min: 400 mg daily
Bumetanide	Bumex	0.5–1.0 mg once or twice daily	1–2 mg once or twice daily	Cl _{cr} 20–50 mL/min: 2 mg once or twice daily Cl _{cr} <20 mL/min: 8–10 mg daily
Torsemide	Demadex	10–20 mg once daily	10–80 mg once daily	Cl _{cr} 20–50 mL/min: 40 mg once daily Cl _{cr} <20 mL/min: 200 mg daily

ACE Inhibitors

Captopril	Capoten	6.25 mg three times daily	50 mg three times daily ^a
Enalapril	Vasotec	2.5 mg twice daily	10–20 mg twice daily ^a
Lisinopril	Zestril, Prinivil	2.5–5 mg once daily	20–40 mg once daily ^a
Quinapril	Accupril	5 mg twice daily	20–40 mg twice daily
Ramipril	Altace	1.25–2.5 mg	5 mg twice daily ^a
Fosinopril	Monopril	5–10 mg once daily	40 mg once daily
Trandolapril	Mavik	0.5–1 mg once daily	4 mg once daily ^a
Perindopril	Aceon	2 mg once daily	8–16 mg once daily

Angiotensin Receptor Blockers

Candesartan	Atacand	4 mg once daily	32 mg once daily ^a
Valsartan	Diovan	20–40 mg twice daily	160 mg twice daily ^a
Losartan	Cozaar	25–50 mg once daily	150 mg once daily ^a

Beta-Blockers

Bisoprolol	Zebeta	1.25 mg once daily	10 mg once daily ^a	Target dose for patients weighing >85 kg is 50 mg twice daily
Carvedilol	Coreg	3.125 mg twice daily	25 mg twice daily ^a	
Carvedilol phosphate	Coreg CR	10 mg once daily	80 mg once daily	
Metoprolol succinate CR/XL	Toprol-XL	12.5–25 mg once daily	200 mg once daily ^a	

Aldosterone Antagonists

Spironolactone	Aldactone	eGFR ≥50 mL/min/1.73m ² : 12.5–25 mg once daily	25–50 mg once daily ^a	eGFR 30–49 mL/min/1.73m ² : 12.5 mg once daily or every other day
Eplerenone	Inspira	eGFR ≥50 mL/min/1.73m ² : 25 mg once daily	50 mg once daily ^a	eGFR 30–49 mL/min/1.73m ² : 25 mg every other day

Other				
Hydralazine- Isosorbide Dinitrate	Bidil	Hydralazine 37.5 mg three times daily Isosorbide dinitrate 20 mg three times daily	Hydralazine 75 mg three times daily ^a Isosorbide dinitrate 40 mg three times daily ^a	
Digoxin	Lanoxin	0.125–0.25 mg once daily	0.125–0.25 mg once daily	Reduce dose in elderly, patients with low lean body mass, and patients with impaired renal function
Ivabradine	Corlanor	5 mg twice daily	5–7.5 mg twice daily	Avoid if resting heart rate <60 BPM before treatment
Sacubitril/valsartan	Entresto	49/51 mg sacubitril/valsartan twice daily	97/103 mg sacubitril/valsartan twice daily ^a	For patients taking a low dose of or not taking an ACEI or ARB or if eGFR is <30 mL/min/1.73m ² , the starting dose is 24/26 mg sacubitril/valsartan twice daily

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

- ACE inhibitors decrease angiotensin II and aldosterone, attenuating many of their deleterious effects, including
 - reducing ventricular remodeling,
 - myocardial fibrosis,
 - myocyte apoptosis,
 - cardiac hypertrophy,
 - norepinephrine release,
 - vasoconstriction, and
 - sodium and water retention.

Cont....

- Clinical trials have documented favorable effects of ACE inhibitors on symptoms, NYHA functional classification, clinical status, HF progression, hospitalizations, and quality of life.
- ACE inhibitors improve survival by 20% to 30% compared with placebo.
- All patients with HFrEF should receive ACE inhibitors unless contraindications are present.
- Post-MI patients without HF symptoms or reduced LVEF (Stage B) should also receive ACE inhibitors to prevent development of HF and to reduce mortality.

Cont....

- Therapy should be started with low doses followed by gradual titration as tolerated to target doses to minimize the risk of hypotension and renal insufficiency
- Renal function and serum potassium should be evaluated at baseline and within 1 to 2 weeks after the start of therapy with periodic assessments thereafter.
- Initiation of β -blocker therapy should not be delayed while the ACE inhibitor is titrated to the target dose because low–intermediate ACE inhibitor doses are equally effective as higher doses for improving symptoms and survival

ANGIOTENSIN RECEPTOR BLOCKERS

- The ARBs block the angiotensin II receptor subtype AT1, preventing the deleterious effects of angiotensin II, regardless of its origin.
- Because they do not affect the ACE enzyme, ARBs do not affect bradykinin, which is linked to ACE inhibitor cough and angioedema.

Cont....

- Although ACE inhibitors remain first-line therapy in patients with Stage C HFrEF, current guidelines recommend use of ARBs in patients unable to tolerate (usually due to cough) ACE inhibitors.
- Combined use of ACE inhibitors, ARBs, and aldosterone antagonists is not recommended because of an increased risk of renal dysfunction and hyperkalemia.

Cont....

- Current guidelines recommend that addition of an ARB can be considered in patients with HFrEF who remain symptomatic despite treatment with an ACE inhibitor and a β -blocker if an aldosterone antagonist cannot be used.
- Although a number of ARBs are available, only candesartan, losartan, and valsartan are recommended because efficacy has been demonstrated in clinical trials.
- As with ACE inhibitors, initial doses should be low with titration to targets achieved in clinical trials

Cont....

- Assess BP, renal function, and serum potassium within 1 to 2 weeks after therapy initiation and dose increases, with these endpoints used to guide subsequent dose changes.
- It is not necessary to reach target ARB doses before adding a β -blocker.
- Caution should be exercised when ARBs are used in patients with angioedema from ACE inhibitors because cross reactivity has been reported.
- ARBs are not alternatives in patients with hypotension, hyperkalemia, or renal insufficiency due to ACE inhibitors because they are just as likely to cause these adverse effects.

β-BLOCKERS

- There is overwhelming clinical trial evidence that certain β-blockers slow disease progression, decrease hospitalizations, and reduce mortality in patients with systolic HF.
- The ACC/AHA guidelines recommend use of β-blockers in all stable patients with HF and a reduced LVEF in the absence of contraindications or a clear history of β-blocker intolerance.

Cont...

- Patients should receive a β -blocker even if symptoms are mild or well controlled with ACE inhibitor and diuretic therapy.
- It is not essential that ACE inhibitor doses be optimized before a β -blocker is started because the addition of a β -blocker is likely to be of greater benefit than an increase in ACE inhibitor dose.

Cont....

- β -Blockers are also recommended for asymptomatic patients with a reduced LVEF (stage B) to decrease the risk of progression to HF.
- 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.
- Titrate to target doses when possible to provide maximal survival benefits.

Cont....

- Carvedilol, metoprolol succinate (CR/XL), and bisoprolol are the only β -blockers shown to reduce mortality in large HF trials.
- Because bisoprolol is not available in the necessary starting dose of 1.25 mg, the choice is typically limited to either carvedilol or metoprolol succinate.
- Initial and target doses are those associated with reductions in mortality in placebo-controlled clinical trials

Cont....

- Doses should be doubled no more often than every 2 weeks, as tolerated, until the target dose or the maximally tolerated dose is reached.
- Patients should understand that dose up-titration is a long, gradual process and that achieving the target dose is important to maximize benefits.
- Further, the response to therapy may be delayed, and HF symptoms may actually worsen during the initiation period.

ALDOSTERONE ANTAGONISTS

- Spironolactone and eplerenone block the mineralocorticoid receptor, the target site for aldosterone.
- In the kidney, aldosterone antagonists inhibit sodium reabsorption and potassium excretion.
- However, diuretic effects are minimal, suggesting that their therapeutic benefits result from other actions.

Cont...

- In the heart, aldosterone antagonists inhibit cardiac extracellular matrix and collagen deposition, thereby attenuating cardiac fibrosis and ventricular remodeling.
- Aldosterone antagonists also attenuate the systemic proinflammatory state, atherogenesis, and oxidative stress caused by aldosterone.

Cont....

- Based on clinical trial results demonstrating reduced mortality, low-dose aldosterone antagonists may be appropriate for:
 - (1) patients with mild to moderately severe HFrEF (NYHA class II–IV) who are receiving standard therapy, and
 - (2) those with LV dysfunction and either acute HF or diabetes early after MI.

Cont....

- Aldosterone antagonists must be used cautiously and with careful monitoring of renal function and potassium concentration.
- They should be avoided in patients with renal impairment, recent worsening of renal function, serum potassium greater than 5 mEq/L, or a history of severe hyperkalemia.

Cont....

- Spironolactone also interacts with androgen and progesterone receptors, which may lead to gynecomastia, impotence, and menstrual irregularities in some patients.
- Initial doses should be low, and doses should be limited to those associated with beneficial effects to decrease the risk for hyperkalemia

Drugs to Consider for Select Patients with HFrEF

NITRATES AND HYDRALAZINE

- **Nitrates (eg, ISDN) and hydralazine have complementary hemodynamic actions.**
- Nitrates are primarily venodilators, producing reductions in preload.
- Hydralazine is a direct arterial vasodilator that reduces systemic vascular resistance (SVR) and increases stroke volume and cardiac output.

Cont...

- The mechanism for the beneficial effects of hydralazine/ISDN in HF remains uncertain but is likely related to normalization of the increased oxidative stress and reduced nitric oxide signaling that contributes to HF progression.

Cont....

- Guidelines recommend addition of hydralazine/ISDN to self-described African Americans with HFrEF and NYHA class III–IV symptoms treated with ACE inhibitors and β -blockers.
- The combination can also be useful in patients unable to tolerate either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or possibly hypotension.

Cont....

- **Obstacles to successful therapy with this drug 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.

ARB/NEPRILYSIN INHIBITOR (ARNI)

- **Valsartan/sacubitril** is an angiotensin receptor/neprilysin inhibitor approved for treatment of HFrEF.
- The drug product is a crystalline complex composed of both drugs.
- Neprilysin is one of the enzymes that break down endogenous natriuretic peptides.

Cont....

- The peptides are beneficial because they cause vasodilation, increased glomerular filtration, natriuresis, and diuresis.
- Sacubitril is a neprilysin inhibitor prodrug that is cleaved into its active form, which inhibits neprilysin thereby promoting vasodilation through a different mechanism than the ARB.
- Combination with valsartan negates the elevated levels of AT2 that would result from use of neprilysin alone

Cont....

- The combination product is indicated to reduce the risk of cardiovascular death and hospitalization for HF in patients with NYHA Class II–IV HF and reduced LVEF.
- When titrated to a target dose of 200 mg (sacubitril 97 mg/valsartan 103 mg) twice daily, the combination reduced the combined endpoint of cardiovascular death and hospitalization for HF by 20% compared to enalapril 10 mg twice daily in patients with symptomatic HF and reduced LVEF.
- Its use will likely be incorporated into future HF guidelines.

IVABRADINE

- **Ivabradine** blocks the If current in the sinoatrial node that is responsible for controlling heart rate, thereby slowing spontaneous depolarization of the sinus node and resulting in a dose-dependent slowing of the heart rate.
- It is indicated to reduce the risk of hospitalization for worsening HF in patients with LVEF $\leq 35\%$ who are in sinus rhythm with resting heart rate ≥ 70 bpm and either are on maximally tolerated doses of β -blockers or have a contraindication to β -blocker use.
- The most common adverse effects are bradycardia, atrial fibrillation, and visual disturbances.

DIGOXIN

- Although digoxin has positive inotropic effects, its benefits in HF are related to its neurohormonal effects.
- Digoxin improves cardiac function, quality of life, exercise tolerance, and HF symptoms in patients with HFrEF but does not improve survival.
- Based on available data, digoxin is not considered a first-line agent in HF, but a trial may be considered in conjunction with GDMT including ACE inhibitors, β -blockers, and diuretics in patients with symptomatic HFrEF to improve symptoms and reduce hospitalizations.

Cont....

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

Cont....

- The target serum digoxin concentration for most patients is 0.5 to 0.9 ng/mL (0.6–1.2 nmol/L).
- Most patients with normal renal function can achieve this level with a dose of 0.125 mg/day.
- Patients with decreased renal function, the elderly, or those receiving interacting drugs (eg, amiodarone) should receive 0.125 mg every other day.

TREATMENT OF ACUTE DECOMPENSATED HEART FAILURE

GENERAL APPROACH

- *Acute decompensated heart failure (ADHF) involves patients with new or worsening signs or symptoms (often resulting from volume overload and/or low cardiac output) requiring medical intervention, such as emergency department visit or hospitalization.*
- **Goals of Treatment:**
 - The overall goal is to relieve symptoms while optimizing volume status and cardiac output so the patient can be discharged in a stable compensated state on oral drug therapy.

Cont....

- Hospitalization should be considered based on clinical findings.
- Most patients may be admitted to a monitored unit or general medical floor.
- 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.

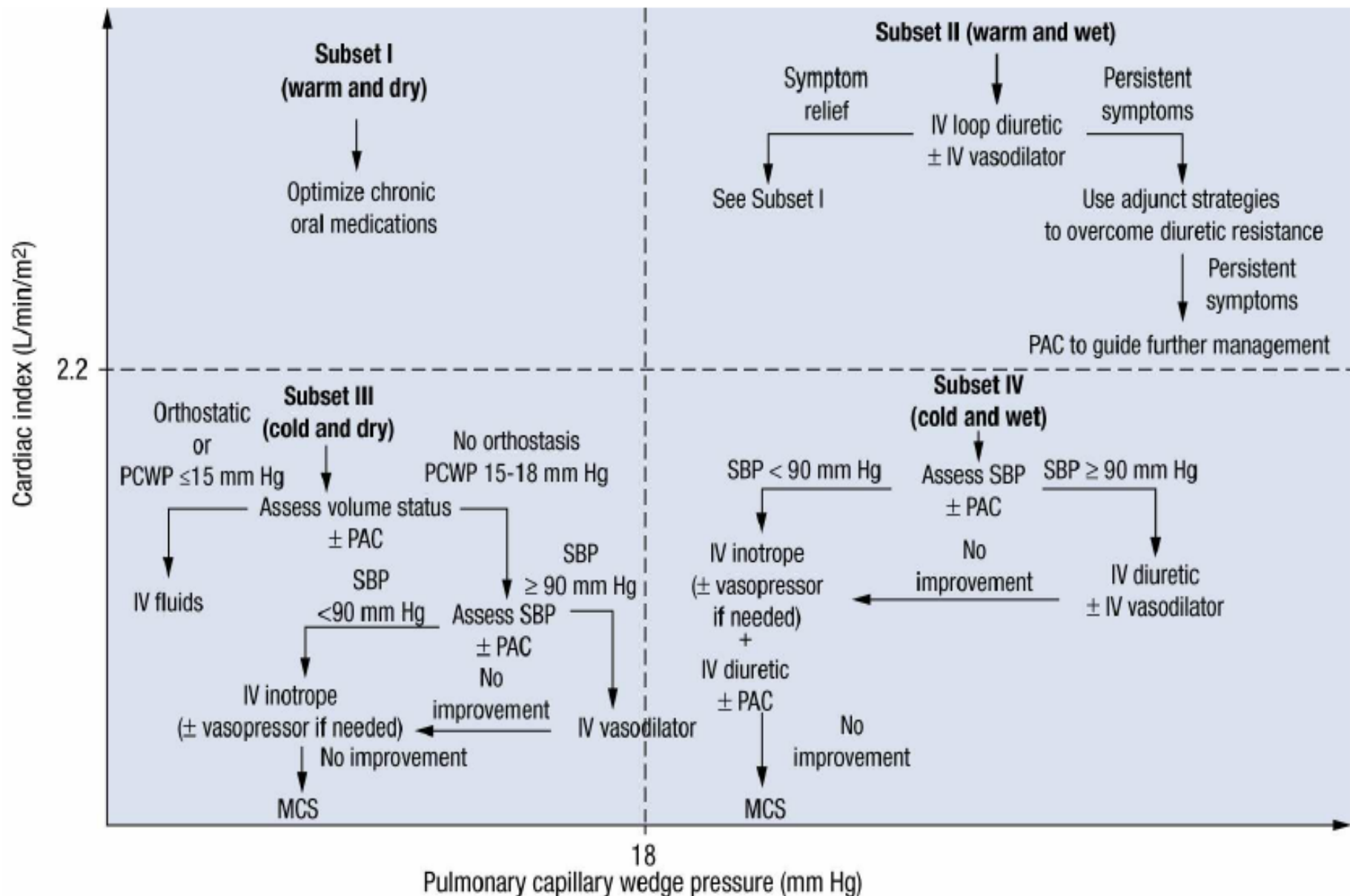
Cont....

- History and physical exam should focus on
 - potential etiologies of ADHF;
 - presence of precipitating factors (eg, arrhythmias, hypertension, myocardial infarction, anemia, and thyroid disorders);
 - onset, duration, and severity of symptoms; and a
 - careful medication history.
- Laboratory tests that may be obtained include BNP or N-terminal pro-BNP, thyroid function tests, complete blood count, cardiac enzymes, and routine serum chemistries.

Cont....

- 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”) and cardiac output (adequate cardiac output or “warm” vs hypoperfusion or “cold”)

General management algorithm for acute decompensated heart failure based on clinical presentation



Cont....

- Reserve invasive hemodynamic monitoring for patients who are refractory to initial therapy, whose volume status is unclear, or who have significant hypotension or worsening renal function despite appropriate initial therapy.
- Address and correct reversible or treatable causes of decompensation.
- Assess medications being taken prior to admission and determine whether adjustment or discontinuation is required.
- If fluid retention is evident on physical exam, pursue aggressive diuresis, often with IV diuretics

Cont....

- 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, neprilysin inhibitors, and aldosterone antagonists) may also need to be temporarily held in the presence of renal dysfunction, with close monitoring of serum potassium.
- Most patients may continue to receive digoxin at doses targeting a trough serum concentration of 0.5 to 0.9 ng/mL (0.6–1.2 nmol/L).

PHARMACOTHERAPY OF ACUTE DECOMPENSATED HEART FAILURE

Diuretics

- IV loop diuretics, including **furosemide, bumetanide, and torsemide, are used for ADHF**, with furosemide being the most widely studied and used agent.
- Bolus administration reduces preload by functional venodilation within 5 to 15 minutes and later (>20 min) via sodium and water excretion, thereby improving pulmonary congestion.
- However, acute reductions in venous return may severely compromise effective preload in patients with significant diastolic dysfunction or intravascular depletion.

Cont....

- Because diuretics can cause excessive preload reduction, they must be used judiciously to obtain the desired improvement in congestive symptoms while avoiding a reduction in cardiac output, symptomatic hypotension, or worsening renal function.
- Diuretic resistance may be overcome by administering larger IV bolus doses or continuous IV infusions of loop diuretics.

Cont....

- Diuresis may also be improved by adding a second diuretic with a different mechanism of action (eg, combining a loop diuretic with a distal tubule blocker such as **metolazone or hydrochlorothiazide**).
- **The loop** diuretic–thiazide combination should generally be reserved for inpatients who can be monitored closely for development of severe electrolyte and intravascular volume depletion.
- In the outpatient setting, very low doses of the thiazide-type diuretic or infrequent administration (eg, 1–3 times weekly) are recommended

Vasodilators

- Venodilators reduce preload by increasing venous capacitance, improving symptoms of pulmonary congestion in patients with high ventricular filling pressures.
- Arterial vasodilators reduce afterload and cause a reflex increase in cardiac output, which may promote diuresis via improved renal perfusion.
- Mixed vasodilators act on both arterial resistance and venous capacitance vessels, reducing congestive symptoms while increasing cardiac output.

NITROGLYCERIN

- **IV nitroglycerin is often preferred for preload reduction in ADHF, especially in patients with pulmonary congestion.**
- It reduces preload and pulmonary capillary wedge pressure (PCWP) via functional venodilation and mild arterial vasodilation.
- 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.

Cont....

- Initiate nitroglycerin at 5 to 10 mcg/min (0.1 mcg/kg/min) and increase every 5 to 10 minutes as necessary and tolerated.
- Maintenance doses usually range from 35 to 200 mcg/min (0.5–3 mcg/kg/min).
- Hypotension and an excessive decrease in PCWP are important dose-limiting side effects.
- Tolerance to the hemodynamic effects may develop over 12 to 72 hours of continuous administration.

NESIRITIDE

- **Nesiritide is a recombinant form of endogenous BNP, which is secreted by the myocardium in response to volume overload.**
- Nesiritide mimics the vasodilatory and natriuretic actions of BNP, resulting in
 - venous and arterial vasodilation;
 - increased cardiac output;
 - natriuresis and diuresis; and
 - decreased cardiac filling pressures, sympathetic nervous system activity, and renin–angiotensin–aldosterone system activity.
- In contrast to nitroglycerin or dobutamine, tolerance to its pharmacologic effects does not develop.

Cont....

- Evidence from clinical trials indicates a limited role for nesiritide beyond relief of congestive symptoms in patients with acute dyspnea.
- Its use for management of ADHF has declined because it produces marginal improvement in clinical outcomes and is substantially more expensive than other IV vasodilators.

NITROPRUSSIDE

- **Sodium nitroprusside is a mixed arteriovenous vasodilator that acts directly on vascular smooth muscle to increase cardiac index and decrease venous pressure to a similar degree as dobutamine and milrinone despite having no direct inotropic activity.**
- However, nitroprusside generally produces greater decreases in PCWP, SVR, and BP.

Cont....

- Hypotension is an important dose-limiting adverse effect of nitroprusside, and its use should be primarily reserved for patients with elevated SVR.
- Close monitoring is required because even modest heart rate increases can have adverse consequences in patients with underlying ischemic heart disease or resting tachycardia.

Cont....

- 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).
- Generally, it does not worsen, and may improve, the balance between myocardial oxygen demand and supply.
- However, an excessive decrease in systemic arterial pressure can decrease coronary perfusion and worsen ischemia.

Cont....

- Nitroprusside has a rapid onset and a duration of action less than 10 minutes, necessitating continuous IV infusions.
- Initiate therapy with a low dose (0.1–0.2 mcg/kg/min) to avoid excessive hypotension, and increase by small increments (0.1–0.2 mcg/kg/min) every 5 to 10 minutes as tolerated.
- Usual effective doses range from 0.5 to 3 mcg/kg/min.

Cont....

- Taper nitroprusside slowly when stopping therapy because of possible rebound after abrupt withdrawal.
- Nitroprusside-induced cyanide and thiocyanate toxicity are unlikely when doses less than 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 $\mu\text{mol/L}$]).

Vasopressin Antagonists

- The vasopressin receptor antagonists currently available affect one or two arginine vasopressin (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.

Cont....

- **Tolvaptan selectively binds to and inhibits the V2 receptor.**
- **It is an oral agent** indicated for hypervolemic and euvolemic hyponatremia in patients with syndrome of inappropriate antidiuretic hormone (SIADH), cirrhosis, and HF.
- Tolvaptan is typically initiated at 15 mg orally daily and then titrated to 30 or 60 mg daily as needed to resolve hyponatremia.
- It is a substrate of cytochrome P450-3A4 and is contraindicated with potent inhibitors of this enzyme.
- The most common side effects are dry mouth, thirst, urinary frequency, constipation, and hyperglycemia.

Cont....

- **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; however, it is not indicated for hyponatremia associated with HF.
- Monitor patients closely to avoid an excessively rapid rise in serum sodium that could cause hypotension or hypovolemia; discontinue therapy if that occurs.
- Therapy may be restarted at a lower dose if hyponatremia recurs or persists and/or these side effects resolve.

Cont....

- The role of vasopressin receptor antagonists in the long-term management of HF is unclear.
- In clinical trials, tolvaptan improved hyponatremia, diuresis, and signs/symptoms of congestion.
- However, one study failed to demonstrate improvement in global clinical status at discharge or a reduction in 2-year all-cause mortality, cardiovascular mortality, or HF rehospitalization

Inotropes

- Low cardiac output in ADHF may worsen renal perfusion, resulting in resistance to diuretic therapy.
- IV inotropes may improve peripheral hypoperfusion and diuresis by improving central hemodynamics.
- However, because of their adverse effect profile they should generally be reserved for patients not responding to other modalities or those with clear evidence of low cardiac output.

Cont....

- Guidelines recommend that inotropes be considered only as a temporizing measure for maintaining end-organ perfusion in patients with cardiogenic shock or evidence of severely depressed cardiac output and low systolic BP (ie, ineligible for IV vasodilators) until definitive therapy can be initiated, as a “bridge” for patients with advanced HF who are eligible for mechanical circulatory support (MCS) or cardiac transplantation, or for palliation of symptoms in patients with advanced HF who are not eligible for MCS or cardiac transplantation.

Cont....

- Dobutamine and milrinone produce similar hemodynamic effects, but dobutamine is usually associated with more pronounced increases in heart rate.

DOBUTAMINE

- **Dobutamine is a β 1- and β 2-receptor agonist with some α 1-agonist effects.**
- **It does** not result in norepinephrine release from nerve terminals, so the positive inotropic effects are attributed to effects on β 1-receptors.
- Stimulation of cardiac β 1-receptors does not generally produce a significant increase in heart rate.
- Modest peripheral β 2-receptor-mediated vasodilation tends to offset minor α 1-receptor-mediated vasoconstriction; the net vascular effect is usually vasodilation.

Cont....

- The initial dose for ADHF is 1 to 2 mcg/kg/min, titrated by 1 to 2 mcg/kg/min every 10 to 20 minutes to a maximum of 20 mcg/kg/min on the basis of clinical and hemodynamic responses.
- Cardiac index is increased because of inotropic stimulation, arterial vasodilation, and a variable increase in heart rate.
- It causes relatively little change in mean arterial pressure compared with the more consistent increases observed with dopamine.
- Although attenuation of dobutamine's hemodynamic effects may occur with prolonged administration, the dobutamine dose should be tapered rather than abruptly discontinued.

MILRINONE

- **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.
- During IV administration, milrinone increases stroke volume and cardiac output with minimal change in heart rate.
- However, the venodilating effects may predominate, leading to decreased BP and a reflex tachycardia.
- Milrinone also lowers pulmonary PCWP by venodilation and is particularly useful in patients with a low cardiac index and elevated LV filling pressure.
- However, this decrease in preload can be hazardous for patients without excessive filling pressure, thus blunting the improvement in cardiac output.

Cont....

- Use milrinone cautiously in severely hypotensive HF patients because it does not increase, and may even decrease, arterial BP.
- Most patients are started on a continuous IV infusion of 0.1 to 0.3 mcg/kg/min, titrated to a maximum of 0.75 mcg/kg/min.
- A loading dose of 50 mcg/kg over 10 minutes can be given if rapid hemodynamic changes are required, but it should generally be avoided because of the risk of hypotension.
- The most notable adverse events are arrhythmia, hypotension, and, rarely, thrombocytopenia. Measure the platelet count before and during therapy.

DOPAMINE

- **Dopamine should generally be avoided in ADHF, but its pharmacologic actions may be preferable to dobutamine or milrinone in patients with marked systemic hypotension or cardiogenic shock in the face of elevated ventricular filling pressures, where dopamine in doses greater than 5 mcg/kg/min may be necessary to raise central aortic pressure.**

Cont....

- Dopamine produces dose-dependent hemodynamic effects because of its relative affinity for $\alpha 1$ -, $\beta 1$ -, $\beta 2$ -, and D1- (vascular dopaminergic) receptors.
- Positive inotropic effects mediated primarily by $\beta 1$ -receptors become more prominent with doses of 2 to 5 mcg/kg/min.
- At doses between 5 and 10 mcg/kg/min, chronotropic and $\alpha 1$ -mediated vasoconstricting effects become more prominent.

Cont....

- Evidence supporting use of low-dose dopamine (2–5 mcg/kg/min) to enhance diuresis is controversial.
- Most studies indicate little if any improvement in urine output, renal protection, or symptom relief, but increased rates of tachycardia.
- Thus, it may not provide any advantage over traditional inotropes in this setting.

MECHANICAL CIRCULATORY SUPPORT

- For patients with refractory ADHF, temporary MCS may be considered for hemodynamic stabilization until the underlying etiology of cardiac dysfunction resolves or has been corrected (“bridge to recovery”) or until evaluation for definitive therapy (eg, durable MCS or cardiac transplantation) can be completed (“bridge to decision”).

Cont....

- Because of its invasive nature and potential complications, MCS should be reserved for patients refractory to maximally tolerated pharmacologic therapy.
- IV vasodilators and inotropes may be used with temporary MCS to maximize hemodynamic and clinical benefits or facilitate device removal.
- Systemic anticoagulant therapy is generally required to prevent device thrombosis, regardless of the method selected.

Cont....

- The **intraaortic balloon pump (IABP)** is **most commonly employed due to ease of use**; however, it only increases cardiac output by about 1 L/min.
- It may be particularly useful for patients with myocardial ischemia complicated by cardiogenic shock, but it has not been shown to improve mortality in this setting.
- **Ventricular assist devices (VADs)** are **surgically implanted and assist, or in some cases replace**, the pumping functions of the right and/or left ventricles.
- Compared to an IABP, VADs confer greater hemodynamic improvements but no differences in long-term survival.

Cont....

- **Extracorporeal membrane oxygenation (ECMO) may be venoarterial or venovenous in nature.**
- In venoarterial ECMO, deoxygenated blood is transported from the venous circulation to an extracorporeal oxygenator and returned as oxygenated blood to the arterial circulation.
- Venovenous ECMO consists of only extracorporeal oxygenation; hemodynamic support is provided by native cardiac function.
- Venoarterial ECMO is more commonly employed in the management of ADHF.

SURGICAL THERAPY

- Orthotopic cardiac transplantation is the best therapeutic option for patients with irreversible advanced HF, as 10-year survival rates approach 60% in patients transplanted after 2001.

EVALUATION OF THERAPEUTIC OUTCOMES CHRONIC HEART FAILURE

- Ask patients about the presence and severity of symptoms and how symptoms affect daily activities.
- Evaluate efficacy of diuretic treatment by disappearance of the signs and symptoms of excess fluid retention.
- Physical examination should focus on body weight, extent of jugular venous distention, presence of hepatojugular reflux, and presence and severity of pulmonary congestion (rales, dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea) and peripheral edema.

Cont....

- Other outcomes are improvement in exercise tolerance and fatigue, decreased nocturia, and a decrease in heart rate.
- Monitor BP to ensure that symptomatic hypotension does not develop as a result of drug therapy.
- Body weight is a sensitive marker of fluid loss or retention, and patients should weigh themselves daily and report changes to their healthcare provider so that adjustments can be made in diuretic doses.

Cont....

- Symptoms may worsen initially on β -blocker therapy, and it may take weeks to months before patients notice symptomatic improvement.
- Routine monitoring of serum electrolytes and renal function is mandatory in patients with HF.

ACUTE DECOMPENSATED HEART FAILURE

- Initial stabilization requires adequate arterial oxygen saturation, cardiac index, and BP.
- **Functional end-organ perfusion** may be assessed by
 - mental status,
 - renal function sufficient to prevent metabolic complications,
 - hepatic function adequate to maintain synthetic and excretory functions,
 - stable heart rate and rhythm,
 - absence of ongoing myocardial ischemia or MI,
 - skeletal muscle and skin blood flow sufficient to prevent ischemic injury, and normal arterial pH (7.34–7.47) and serum lactate concentration.

Cont....

- These goals are most often achieved with a cardiac index greater than 2.2 L/min/m², mean arterial BP greater than 60 mm Hg, and PCWP 15 mm Hg or greater.
- Daily monitoring should include weight, strict fluid intake and output measurements, and HF signs/symptoms to assess the efficacy of drug therapy.
- Monitoring for electrolyte depletion, symptomatic hypotension, and renal dysfunction should be performed frequently.

Cont...

- Vital signs should be assessed frequently throughout the day.
- Patients should not be discharged until optimal volume status is achieved and the patient is successfully transitioned from IV to oral diuretics, GDMT is stable, and IV inotropes and vasodilators have been discontinued for at least 24 hours.

Cont....

- Thank you!