

Heart Failure

Learning Objectives

Upon completion of the chapter, the reader will be able to:

- Differentiate between the common underlying etiologies of heart failure, including ischemic, non-ischemic, and idiopathic causes.
- Describe the pathophysiology of heart failure as it relates to neurohormonal activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system.
- Identify signs and symptoms of heart failure

- Describe the goals of therapy for a patient with acute or chronic heart failure.
- Develop a nonpharmacologic treatment plan which includes patient education for managing heart failure.
- Develop a specific evidence-based pharmacologic treatment plan for a patient with acute or chronic heart failure based on disease severity and symptoms.
- Formulate a monitoring plan for the nonpharmacologic and pharmacologic treatment of a patient with heart failure.

- **Heart failure (HF)**

- is defined as the inadequate ability of the heart to pump enough blood to meet the blood flow and metabolic demands of the body.

Epidemiology and Etiology

Epidemiology

- Heart failure is a major public health concern affecting approximately five million people in the United States.
- An additional 550,000 new cases are diagnosed each year.
- Heart failure manifests most commonly in adults over the age of 60.

Etiology

- The most common causes of HF are
 - Coronary artery disease (CAD)
 - Hypertension
 - Dilated cardiomyopathy.
- A normal cardiac cycle is dependent on two components:
 - systole and diastole.
- **Expulsion** of blood occurs during **systole** or **contraction** of the ventricles

- **Ejection fraction (EF)** is the fraction of the volume present at the end of diastole that is pushed into the aorta during systole.

Pathophysiology

- Cardiac output
 - is defined as the volume of blood ejected per unit of time (liters per minute)
 - is a major determinant of tissue perfusion.

Heart rate

- Rate at which the heart contracts to pump blood around the body
- In most people, heart rate is between 60 and 100 beats per minute at rest.
- Very fit people may have a rate below 60 beats per minute.

- Cardiac output is the product of heart rate (HR) and stroke volume (SV):
 - $CO = HR \times SV$.
- Stroke volume
 - is the volume of blood ejected with each systole.
 - is determined by factors regulating preload, afterload, and contractility.

Preload

- is a measure of ventricular filling pressure, or the volume of blood in the left ventricle (also known as LV end diastolic volume).
- is determined by venous return as well as atrial contraction.

- **Afterload** is the resistance to ventricular ejection

Compensatory Mechanisms

- In the setting of a sustained loss of myocardium, a number of mechanisms aid the heart when faced with an increased hemodynamic burden and reduced CO.
- They include the following:
 - Frank-Starling mechanism
 - tachycardia and increased afterload
 - cardiac hypertrophy and remodeling

Preload and the Frank-Starling Mechanism

- In the setting of a sudden decrease in CO, the natural response of the body is to decrease blood flow to the periphery
 - in order to maintain perfusion to the vital organs such as the heart and brain.
- Therefore, renal perfusion is compromised due to both the decreased CO, as well as shunting of blood away from peripheral tissues.
- This results in activation of the RAAS
 - production of angiotensin II
 - synthesis and release of aldosterone

- In a healthy heart, a large increase in CO is usually accomplished with just a small change in preload.
- In a failing heart, alterations in the contractile filaments reduce the ability of cardiomyocytes to adapt to increases in preload.
- Thus, an increase in preload actually impairs contractile function in the failing heart and results in a further decrease in CO.

Tachycardia and Increased Afterload

- Another mechanism to maintain CO when contractility is low is to increase heart rate.

- This is achieved through sympathetic nervous system (SNS) activation and the agonist effect of norepinephrine on β -adrenergic receptors in the heart
- Activation of both the RAAS and the SNS also contribute to vasoconstriction
- However, arterial vasoconstriction leads to impaired forward ejection of blood from the heart due to an increase in afterload.
- This results in a decrease in CO and continued stimulation of compensatory responses

Cardiac Hypertrophy and Remodeling

- Ventricular hypertrophy, an adaptive increase in ventricular muscle mass due to
 - growth of existing myocytes, occurs in response to an increased hemodynamic burden such as volume or pressure overload
- Cardiac remodeling occurs as a compensatory adaptation to a change in wall stress
- Even after remodeling occurs, the heart can maintain CO for many years.
 - However, heart function will continue to deteriorate until progression to clinical HF.

Beneficial and Detrimental Effects of the Compensatory Responses in Heart Failure

Compensatory Response	Beneficial Effects of Compensation	Detrimental Effects of Compensation
Increased preload (through sodium and water retention)	Optimize stroke volume via Frank-Starling mechanism	Pulmonary and systemic congestion and edema formation Increased MVO2
Vasoconstriction	Maintain blood pressure and perfusion in the face of reduced cardiac output volume	Increased MVO2 Increased afterload decreases stroke volume and further activates the compensatory responses
Tachycardia and increased contractility (due to SNS activation)	Increase cardiac output	Increased MVO2 Shortened diastolic filling time β 1-Receptor down-regulation, decreased receptor sensitivity Precipitation of ventricular arrhythmias Increased risk of myocardial cell death
Ventricular	Maintains cardiac	Diastolic dysfunction

MVO2, myocardial oxygen consumption; SNS, sympathetic nervous system.

Models of Heart Failure

- Earlier models of HF focused on the hemodynamic consequences of volume overload
 - from excess sodium and water retention, decreased CO secondary to impaired ventricular function, and vasoconstriction.
- Congestion was a result of fluid backup due to inadequate pump function.
- Therefore, drug therapy was focused on relieving excess volume
 - using diuretics, improving pump function with inotropic agents, and alleviating vasoconstriction with vasodilators.

- Although these agents improved HF symptoms
 - they did little to slow the progressive decline in cardiac function or to improve survival.

Neurohormonal Model

- Development and progression of HF involves activation of neurohormonal pathways including
 - the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).

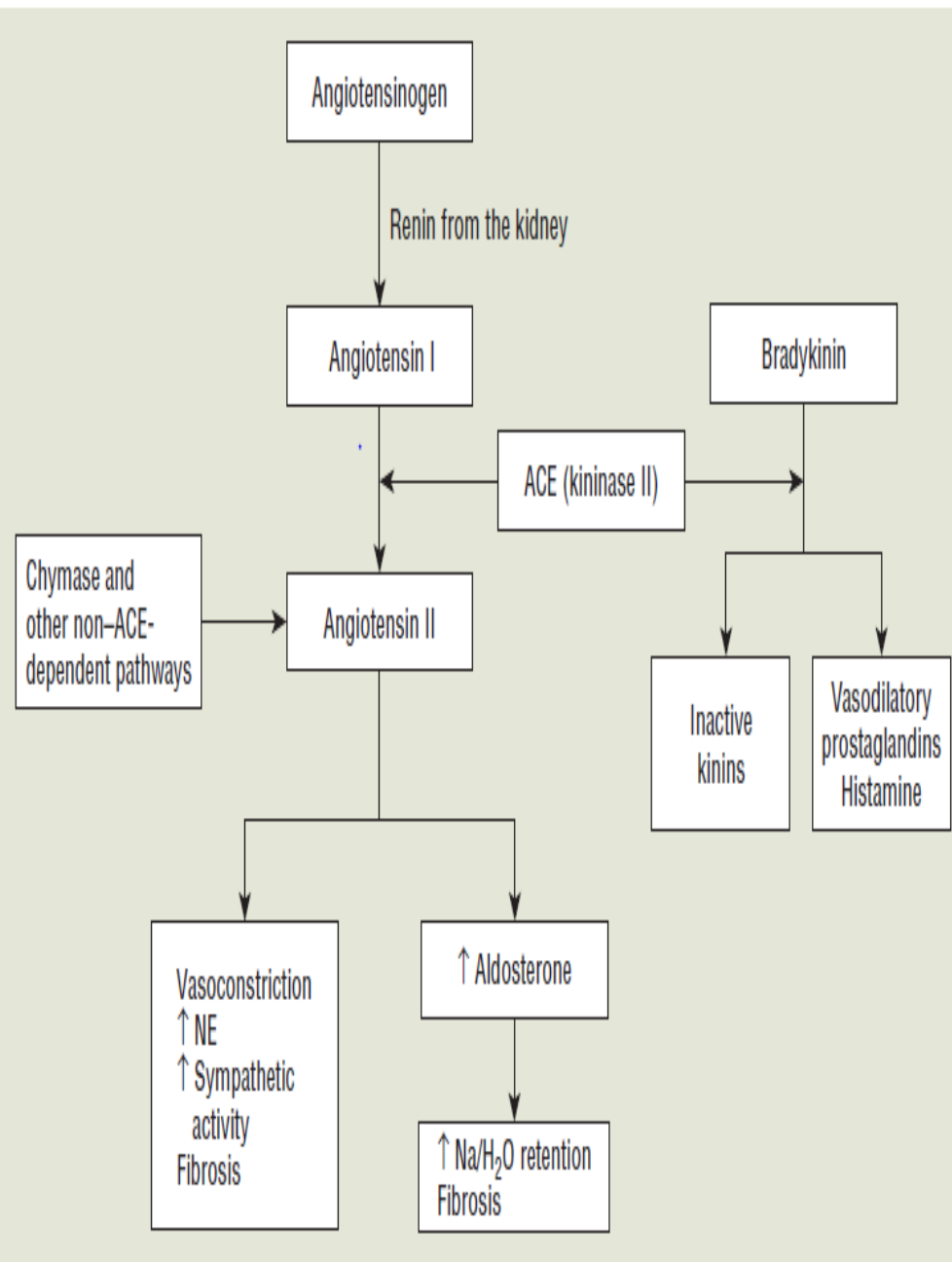
- This model begins with an initial precipitating event or myocardial injury
 - resulting in a decline in CO, followed by the compensatory mechanisms.
- This includes activation of neurohormonal pathways with pathologic consequences including
 - RAAS, SNS, endothelin and vasopressin, and those with counterregulatory properties such as the natriuretic peptides and nitric oxide.

- This model currently guides our therapy for chronic HF in terms of preventing disease progression and mortality.

Angiotensin II

- Angiotensin II is a key neurohormone in the pathophysiology of HF
- The vasoconstrictive effects of angiotensin II lead to
 - an increase in systemic vascular resistance (SVR) and blood pressure
- The resulting increase in afterload contributes to
 - an increase in myocardial oxygen demand and opposes the desired increase in SV

- In the kidneys, angiotensin II enhances renal function acutely by
 - raising intraglomerular pressure through constriction of the efferent arterioles.
- However, the increase in glomerular filtration pressure may be offset by
 - a reduction in renal perfusion secondary to angiotensin II's influence over the release of other vasoactive neurohormones such as vasopressin and endothelin-1 (ET-1).
- Angiotensin II also potentiates the release of aldosterone from the adrenal glands and norepinephrine from adrenergic nerve terminals



- Physiology of the renin-angiotensin-aldosterone system.
- Renin produces angiotensin I from angiotensinogen.
- Angiotensin I is cleaved to angiotensin II by angiotensin-converting enzyme (ACE).
- Angiotensin II has a number of physiologic actions that are detrimental in heart failure.
- ACE is also responsible for the breakdown of bradykinin.
- Inhibition of ACE results in accumulation of bradykinin that, in turn, enhances the production of vasodilatory prostaglandins. (NE, norepinephrine.)

- Angiotensin II induces vascular hypertrophy and remodeling in both cardiac and renal cells.
- Clinical studies show that blocking the effects of the RAAS in HF
 - is associated with improved cardiac function and prolonged survival.
- Thus, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)
 - are the cornerstone of HF treatment.

Aldosterone

- Aldosterone's contribution to HF pathophysiology is also multifaceted.

- Renally, aldosterone causes sodium and water retention in an attempt to enhance intravascular volume and CO.
- This adaptive mechanism has deleterious consequences since excessive sodium and water retention worsen the already elevated ventricular filling pressures.
- Aldosterone also contributes to electrolyte abnormalities seen in HF patients.
- Hypokalemia and hypomagnesemia contribute to the increased risk of arrhythmias.

- Thus, aldosterone antagonism has become an important therapeutic target for improvement of long-term prognosis.

Norepinephrine

- Norepinephrine is a classic marker for SNS activation.
- It plays an adaptive role in the failing heart by stimulating HR and myocardial contractility to augment CO and by producing vasoconstriction to maintain organ perfusion.
- Excess levels are directly cardiotoxic.
- Plasma norepinephrine concentrations are elevated proportionally to HF severity

- β -Adrenergic blocking agents have become an essential therapy for chronic HF.

Endothelin

- One of the most potent physiologic vasoconstrictors
- Is an important contributor to HF pathophysiology.

Arginine Vasopressin

- Vasopressin exerts its effects through vasopressin type 1a (V1a) and vasopressin type 2 (V2) receptors.
- Vasopressin type 1a stimulation leads to vasoconstriction

- Vasopressin type 2 receptor cause free water retention.
- Vasopressin increases preload, afterload, and myocardial oxygen demand in the failing heart.

Counterregulatory Hormones (Natriuretic Peptides, Bradykinin, and Nitric Oxide)

- Atrial natriuretic peptide (ANP) and B-type (formerly brain) natriuretic peptide (BNP)
 - are endogenous neurohormones that regulate sodium and water balance.
- Natriuretic peptides decrease sodium reabsorption

- Natriuretic peptides also cause vasodilation
- Higher concentrations of natriuretic peptides correlate with a more severe HF
- Bradykinin levels are elevated in HF patients
- Nitric oxide
 - a vasodilatory hormone released by the endothelium
 - is found in higher concentrations in HF

Clinical Presentation Heart Failure

Symptoms

- Dyspnea(difficulty or pain in breathing)
- Orthopnea(difficulty in breathing while lying down)
- Shortness of breath (SOB)
- Paroxysmal nocturnal dyspnea(attack of breathlessness at night)
- Exercise intolerance
- Tachypnea
- Cough
- Nocturia and/or polyuria
- Hemoptysis
- Abdominal pain
- Anorexia
- Nausea
- Bloating
- Ascites
- Mental status changes
- Weakness

Signs

- Pulmonary edema
- Tachycardia
- Cardiomegaly
- Peripheral edema (e.g., pedal edema, which is swelling of feet and ankles)
- Jugular venous distension (JVD)
- Hepatomegaly

Drugs That May Precipitate or Exacerbate Heart Failure

Agents Causing Negative Inotropic Effect

- Antiarrhythmics (e.g., disopyramide, flecainide, and others)
- β -Blockers (e.g., propranolol, metoprolol, atenolol, and others)
- Calcium channel blockers (e.g., verapamil and others)
- Itraconazole

Cardiotoxic Agents

- Doxorubicin

Agents Causing Sodium and Water Retention

- Non-steroidal anti-inflammatory drugs
- COX-2 inhibitors
- Sodium-containing drugs (e.g., carbenicillin disodium, ticarcillin disodium)

Heart Failure Classification

- There are two common systems for categorizing patients with HF.
- The New York Heart Association (NYHA) Functional Classification (FC) system
 - is based on the patient's activity level and exercise tolerance.
- The American College of Cardiology/American Heart Association (ACC/AHA) has proposed another system
 - based on the development and progression of the disease
 - Instead of classifications, patients are placed into stages

- Patients can move between NYHA functional classes as symptoms improve with treatment
- Whereas HF staging does not allow for patients to move to a lower stage
 - e.g., patients cannot be categorized as stage C and move to stage B after treatment.

New York Heart Association (NYHA) Functional Classification and American College of Cardiology/American Heart Association (ACC/AHA) Staging

NYHA Functional Class	ACC/AHA Stage	Description
N/A	A	Patients at high risk for heart failure but without structural heart disease or symptoms of heart failure
I	B	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	C	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical

III	C	Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	C, D	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of heart failure are present at rest. With any physical activity, increased discomfort is experienced. Stage D refers to end-stage heart failure patients.

Treatment of chronic heart failure

Desired Therapeutic Outcomes

- There is no cure for HF.
- The general management goals for chronic HF include
 - preventing the onset of clinical symptoms or reducing symptoms
 - preventing or reducing hospitalizations
 - slowing progression of the disease
 - improving quality of life
 - prolonging survival.

Nonpharmacologic Interventions

- Nonpharmacologic treatment involves dietary modifications
 - such as sodium and fluid restriction, risk factor reduction including smoking cessation, and supervised regular physical activity.
- Patient education regarding monitoring symptoms, dietary and medication adherence, risk factor reduction, are important for prevention of AHF exacerbations.

Pharmacologic Treatment

Diuretics

- Diuretics are used for relief of acute symptoms of congestion and maintenance of euvolemia(normal amount of blood)
- Diuretic therapy is recommended for all patients with clinical evidence of fluid overload retention
- Two types of diuretics are used for volume management in HF:
 - thiazides and loop diuretics.

- Thiazide diuretics such as hydrochlorothiazide, chlorthalidone, and metolazone
 - block sodium and chloride reabsorption in the distal convoluted tubule
- Thiazides are weaker than loop diuretics
 - in terms of effecting an increase in urine output and therefore are not utilized frequently as monotherapy in HF.
- Loop diuretics are the most widely used diuretics in HF.
 - These agents, including furosemide, bumetanide, and torsemide, exert their action at the thick ascending loop of Henle.

- Loop diuretics increase sodium and water excretion
- Oral diuretic efficacy may vary based on differing **bioavailability**
 - almost complete for torsemide and bumetanide
 - but averages only 50% for furosemide.
- Therefore, oral torsemide can be considered an alternative to the intravenous route of administration
 - for patients who do not respond to oral furosemide in the setting of profound edema.

- The onset of effect is slightly delayed after oral administration but occurs within a few minutes with intravenous dosing.
- bioequivalent doses of intravenous furosemide are half the oral dose
- bumetanide and torsemide intravenous doses are generally equivalent to the oral doses.
- Diuretics cause numerous adverse effects.
- A particularly worrisome adverse effect in the setting of HF is hypokalemia
 - Low serum potassium can predispose patients to arrhythmias and sudden death.

- Hypomagnesemia often occurs concomitantly with diuretic-induced hypokalemia
 - therefore both should be assessed and replaced in patients needing correction of hypokalemia.
- Magnesium is an essential co-factor for movement of potassium intracellularly to restore body stores.

Neurohormonal Blocking Agents

- Agents with proven benefits in improving symptoms, slowing disease progression, and improving survival in chronic HF
 - target neurohormonal blockade.

- These include ACE inhibitors, ARBs, b-adrenergic blockers, and aldosterone antagonists.

Angiotensin-Converting Enzyme Inhibitors

- ACE inhibitors are the cornerstone of treatment for HF.
- ACE inhibitors decrease neurohormonal activation by blocking the conversion of angiotensin I (AT1) to angiotensin II (AT2)
 - A potent mediator of vasoconstriction and cardiac remodeling.
- The breakdown of bradykinin is also reduced.
- Bradykinin enhances the release of vasodilatory prostaglandins and histamines.

- These effects result in
 - arterial and venous dilatation
 - decrease in myocardial workload through reduction of both preload and afterload.
- ACE inhibitors significantly reduce hospitalization rates and mortality regardless of underlying disease severity or etiology.
- ACE inhibitors are also effective in preventing HF development in high-risk patients.
- ACE inhibition decreases the risk of HF hospitalization and death in patients with asymptomatic LV dysfunction.

- Studies in acute MI patients show a reduction in new-onset HF and death with ACE inhibitors whether they are initiated early (within 36 hours) or started later.
- All patients with documented LV systolic dysfunction, regardless of existing HF symptoms, should receive ACE inhibitors unless a contraindication or intolerance is present.
- ACE inhibitors should be initiated using low

- Despite their clear benefits, ACE inhibitors are still underutilized in HF.
- One reason is undue concern or confusion regarding absolute versus relative contraindications for their use.
- Absolute contraindications include a history of angioedema, bilateral renal artery stenosis, and pregnancy.
- Relative contraindications include unilateral renal artery stenosis, renal insufficiency,

- Hypotension occurs commonly at the initiation of therapy or with dosage increases but may happen anytime during therapy.
- Hypotension can manifest as dizziness, lightheadedness, syncope.
- The risk of hypotension due to possible volume depletion increases
 - when ACE inhibitors are initiated or used concomitantly in patients on high diuretic doses.
- Therefore, in euvolemic patients, diuretic doses may often be decreased or withheld during ACE inhibitor dose titration.

- Initiating at a low dose and titrating slowly can also minimize hypotension.
- It may be advisable to initiate therapy with a short-acting ACE inhibitor, such as captopril, and subsequently switch to a longer-acting agent, such as lisinopril or enalapril, once the patient is stabilized.
- Hyperkalemia results from reduced angiotensin II-stimulated aldosterone release.
- To minimize hyperkalemia, patients should be counseled to avoid foods high in potassium such as certain salt substitutes.

- ACE inhibitor dose may need to be decreased or held if serum potassium increases above 5 mEq/L (5 mmol/L).
- Cough is commonly seen with ACE inhibitors (5% to 15%)
 - may be related to accumulation of tissue bradykinins.
- It can be challenging to distinguish an ACE inhibitor-induced cough from cough caused by pulmonary congestion.
- A productive or wet cough usually signifies congestion
- Dry, hacking cough is more indicative of a drug-related etiology.
- If a cough is determined to be ACE inhibitor-induced, its severity should be evaluated before deciding on a course of action.

- If the cough is truly bothersome, a trial with a different ACE inhibitor or switching to an ARB is warranted.

Angiotensin Receptor Blockers

- Angiotensin receptor blockers selectively antagonize the effects of angiotensin II directly at the AT1 receptor.
- AT1 receptor stimulation is associated with
 - vasoconstriction, release of aldosterone, and cellular growth promoting effects
- Angiotensin receptor type 2 (AT2) stimulation causes vasodilation

- Bilateral renal artery stenosis is an absolute contraindication to ARB therapy unless it has been corrected.
- Neither ACE inhibitors nor ARBs should be used in patients
 - who are pregnant or actively trying to become pregnant because of associated teratogenicity
- In patients truly intolerant or contraindicated to ACE inhibitors or ARBs
 - the combination of hydralazine and isosorbide dinitrate should be considered.

Hydralazine and Isosorbide Dinitrate

- Complementary hemodynamic actions originally led to the combination of nitrates with hydralazine.
- Nitrates reduce preload by causing primarily venous vasodilation
 - through activating guanylate cyclase and a subsequent increase in cyclic guanosine monophosphate (cGMP) in vascular smooth muscle.
- Hydralazine reduces afterload through direct arterial smooth muscle relaxation via an unknown mechanism.

- The combination of hydralazine and isosorbide dinitrate was the first therapy shown to improve long-term survival in patients with systolic HF
 - but has largely been supplanted/replaced by angiotensin II antagonist therapy
- Therefore, this combination therapy was reserved for patients
 - intolerant to ACE inhibitors or ARBs secondary to renal impairment, angioedema, or hyperkalemia.

Beta-Adrenergic Antagonists

- Beta-adrenergic antagonists, or β -blockers, competitively block the influence of the SNS at β -adrenergic receptors.

- To date, only three β - blockers have been shown to reduce mortality in systolic HF, including
 - the selective β_1 -antagonists bisoprolol and metoprolol succinate,
 - the non-selective β_1 -, β_2 -, and α_1 -antagonist carvedilol
- Several smaller studies and a metaanalysis suggested that
 - carvedilol increased left ventricular ejection fraction (LVEF), improved cardiac hemodynamics, and slowed remodeling to a greater extent than metoprolol tartrate.
- One study compared immediate-release metoprolol tartrate to carvedilol in 3,000 patients with mild to severe HF.

- Carvedilol lowered all-cause mortality significantly more than metoprolol tartrate.

Aldosterone Antagonists

- Currently, the aldosterone antagonists available are spironolactone and eplerenone.
- Both agents are inhibitors of aldosterone that produce
 - weak diuretic effects while sparing potassium concentrations.

- Each agent (spironolactone and eplerenone) has been studied in a defined population of patients with HF.
- One study established efficacy with low-dose spironolactone in NYHA FC III and IV heart failure patients in reducing HF
 - hospitalizations, improving functional class, reducing sudden cardiac death, and improving all-cause mortality.
- Another study investigated the use of eplerenone in patients within 14 days of MI and LVEF less than 40%.

- Eplerenone was found to decrease mortality as well as cardiovascular death and related hospitalization, mainly due to reducing occurrence of sudden cardiac death.
- Based on these two studies, the ACC/AHA guidelines recommend that the addition of spironolactone be considered in NYHA FC III and IV (ACC/AHA stages C and D) patients, and eplerenone in directly post-MI patients with evidence of LV dysfunction
- The major risk related to aldosterone antagonists is hyperkalemia

- Before and within one week of initiating therapy, two parameters must be assessed:
 - serum potassium and creatinine clearance (or serum creatinine).
- Aldosterone antagonists should not be initiated in patients with potassium concentrations greater than 5.5 mEq/L (5.5 mmol/L).
- These agents should not be given when creatinine clearance is less than 30 mL/minute

- Other adverse effects observed mainly with spironolactone include
 - gynecomastia for men
 - breast tenderness and menstrual irregularities for women.
- Gynecomastia leads to discontinuation in up to 10% of patients on spironolactone.

Digoxin

- Digoxin was shown to decrease HF-related hospitalizations but did not decrease HF progression or improve survival
- Digoxin is initiated at a dose of 0.125 to 0.25 mg daily depending on age, renal function, and risk for toxicity.

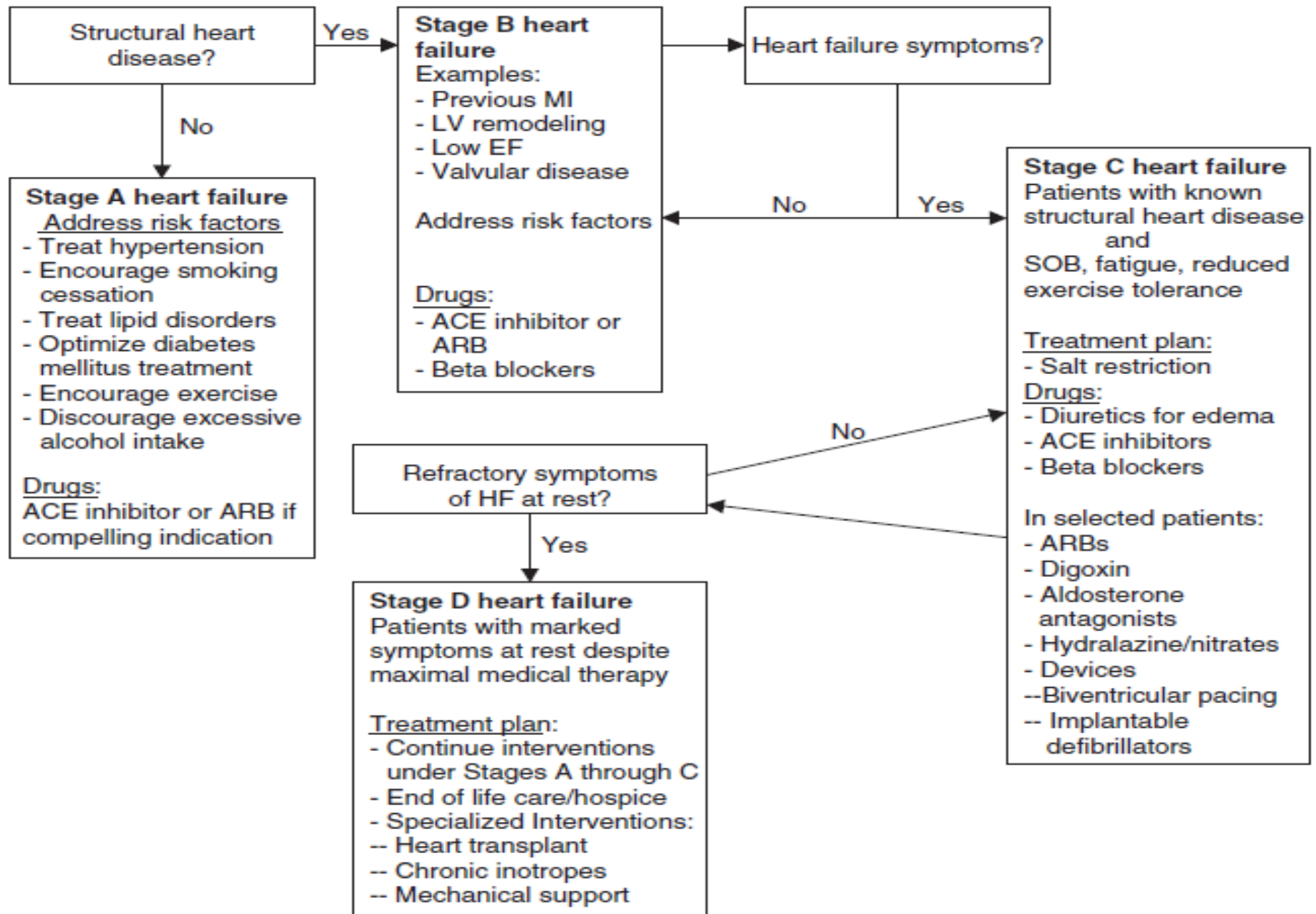
- The 0.125 mg daily dose is adequate in the majority of patients.

Calcium Channel Blockers

- Treatment with nondihydropyridine calcium channel blockers (diltiazem and verapamil)
 - may worsen HF and increase the risk of death in patients with advanced LV dysfunction due to their negative inotropic effects.
- Dihydropyridine calcium channel blockers, although negative inotropes in vitro, do not appear to decrease contractility in vivo.
- Amlodipine and felodipine are the two most extensively studied dihydropyridine calcium channel blockers for systolic HF.

- These two agents have not been shown to affect patient survival, either positively or negatively.
- As such, they are not routinely recommended as part of a standard HF regimen
 - however, amlodipine and felodipine can safely be used in HF patients to treat uncontrolled hypertension or angina once all other appropriate drugs are maximized.

Treatment algorithm for chronic heart failure.



Outcome Evaluation of Chronic Heart Failure

- The evaluation of therapy is influenced by the ability of treatment
 - to successfully reduce symptoms, improve quality of life, decrease frequency of hospitalizations for AHF, reduce disease progression, and prolong survival.
- Assess symptoms of HF such as dyspnea on exertion, orthopnea, weight gain, and edema
- If diuretic therapy is warranted, monitor for therapeutic response by assessing weight loss and improvement of fluid retention
- Monitor blood pressure to evaluate for hypotension caused by drug therapy.