الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

السنة الثالثة

تأثير الأدوية 2

د.رامز ونوس

المحاضرة 12

Heart failure (HF)

Dr. Ramez wannous

Heart failure (HF)

- A complex progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.
- HF is due to an impaired ability of the heart to adequately fill with and/or eject blood.
- It is often accompanied by abnormal increases in blood volume and interstitial fluid.
- symptoms : dyspnea, fatigue, and fluid retention.
- Risk of death is 5-10% annually in patients with mild symptoms and increases to as high as 30-40% annually in patients with advanced disease

Heart Failure

- Final common pathway for many cardiovascular diseases whose natural history results in symptomatic or asymptomatic left ventricular dysfunction
- Underlying causes of HF include arteriosclerotic heart disease, myocardial infarction, hypertensive heart disease, valvular heart disease, and congenital heart disease
- Goals of treatment are to alleviate symptoms, slow disease progression, and improve survival.

Compensatory physiological responses in HF

- Sympathetic nervous system
- Renin–angiotensin–aldosterone
- Myocardial hypertrophy

Compensatory physiological responses in HF

- **Increased sympathetic activity:**

- Baroreceptors sense a decrease in blood pressure and activate the sympathetic nervous system.
- Stimulation of β-adrenergic receptors results in an increased heart rate and a greater force of contraction of the heart muscle.
- Stimulation of α1-adrenergic receptors leads to vasoconstriction which enhances venous return and increases cardiac preload.
  An increase in preload (stretch on the heart) increases stroke volume, which, in turn, increases cardiac output.
- This compensatory response increases the work of the heart, which, in the long term, contributes to further decline in cardiac function.

- **Activation of the renin–angiotensin–aldosterone system:**

- A fall in cardiac output decreases blood flow to the kidney, prompting the release of renin, and resulting in increased formation of angiotensin II and release of aldosterone.
- This results in increased peripheral resistance (afterload) and retention of sodium and water.
- Blood volume increases, and more blood is returned to the heart. If the heart is unable to pump this extra volume, venous pressure increases and peripheral and pulmonary edema occur.
- This compensatory response increases the work of the heart, contributing to further decline in cardiac function.

- **Myocardial hypertrophy:**
- The heart increases in size, and the chambers dilate and become more globular.
- Initially, stretching of the heart muscle leads to a stronger contraction of the heart. However, excessive elongation of the fibers results in weaker contractions, and the geometry diminishes the ability to eject blood.
- This type of failure is termed "systolic failure" or HF with reduced ejection fraction (HFrEF) and is the result of the ventricle being unable to pump effectively.
- Less commonly, patients with HF may have "diastolic dysfunction," a term applied when the ability of the ventricles to relax and accept blood is impaired by structural changes such as hypertrophy. The thickening of the ventricular wall and subsequent decrease in ventricular volume decrease the ability of heart muscle to relax. In this case, the ventricle does not fill adequately, and the inadequacy of cardiac output is termed "diastolic HF" or HF with preserved ejection fraction (HFnEF).

Therapeutic strategies in HF

Chronic HF :

- fluid limitations (less than 1.5 to 2 L daily)
- low dietary intake of sodium (less than 2000 mg/d)
- Diuretics
- Inhibitors of the renin–angiotensin–aldosterone system
- Inhibitors of the sympathetic nervous system.

Acute HF:

- + Inotropic agents

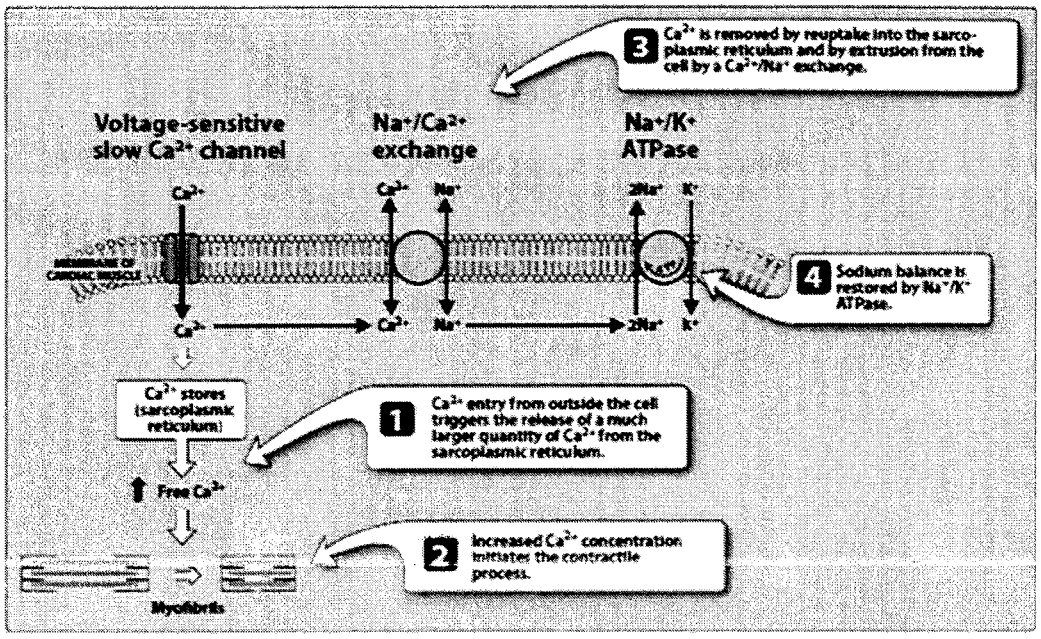
- Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol and nondihydropyridine calcium channel blockers should be avoided if possible.

Drugs in HF

- 1) ACE inhibitors
- 2) angiotensin-receptor blockers
- 3) aldosterone antagonists
- 4) β-blockers
- 5) diuretics
- 6) direct vaso- and venodilators
- 7) inotropic agents

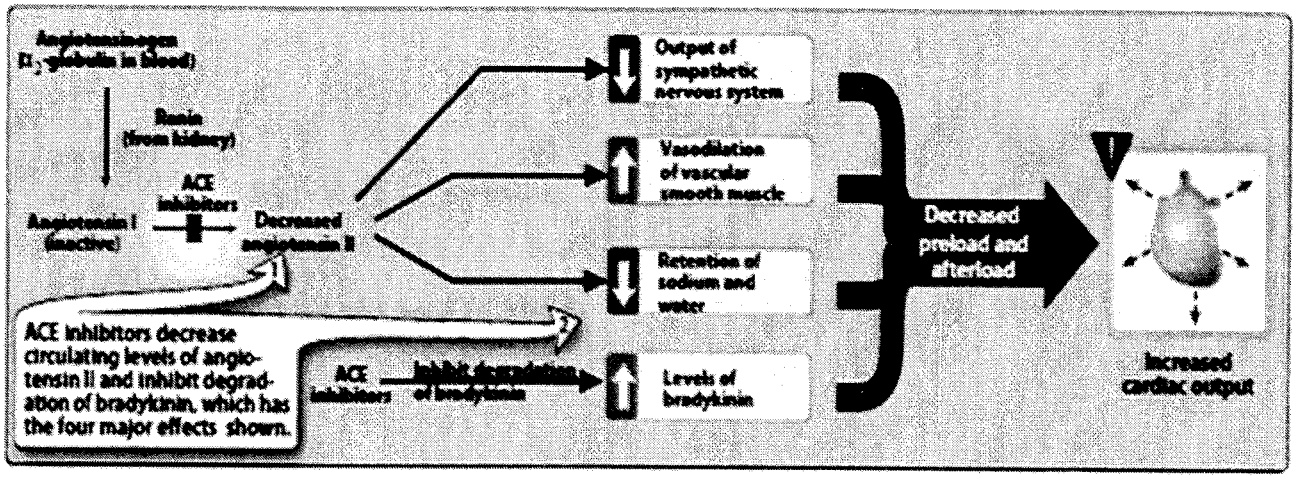
- One or more of these classes of drugs are administered depending on the severity of HF and individual patient factors.
- Pharmacologic intervention provides the following benefits in HF:
  - reduced myocardial work load by decreasing extracellular fluid volume
  - improved cardiac contractility
  - reduced rate of cardiac remodeling.

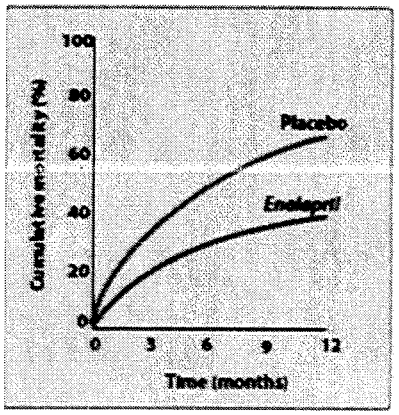
- Knowledge of the physiology of cardiac muscle contraction is essential for understanding the compensatory responses evoked by the failing heart, as well as the actions of drugs used to treat HF.



Angiotensin-converting enzyme (ACE) inhibitors

- Are a part of standard pharmacotherapy in HFrEF
- ACE inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output.
- ACE inhibitors also blunt the usual angiotensin II–mediated increase in aldosterone seen in HF.
- ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF





- ACE inhibitors are indicated for patients with all stages of left ventricular failure.
- Patients with the lowest ejection fraction show the greatest benefit from use of ACE inhibitors.
- Depending on the severity of HF, ACE inhibitors may be used in combination with diuretics, β-blockers, *digoxin, aldosterone antagonists, and hydralazine/isosorbide dinitrate.*
- Used in Patients who have had a recent myocardial infarction, hypertension or are at high risk for a cardiovascular.

Pharmacokinetics

- ACE inhibitors are adequately absorbed following oral administration. Food may decrease the absorption of *Captopril, so it should be taken on an empty stomach.*
- Except for *captopril, ACE inhibitors are prodrugs that require* activation by hydrolysis via hepatic enzymes.
- Renal elimination of the active moiety is important for most ACE inhibitors except *fosinopril.*
- *Plasma half-lives of active compounds* vary from 2 to 12 hours, although the inhibition of ACE may be much longer.

Adverse effects:

- postural hypotension, renal insufficiency, hyperkalemia, a persistent dry cough, and angioedema (rare).
- ACE inhibitors are teratogenic and should not be used in pregnant women.

Angiotensin receptor blockers

- Angiotensin receptor blockers (ARBs) are orally active compounds that are competitive antagonists of the angiotensin II type 1 receptor.
- ARBs do not affect bradykinin levels.
- Although ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical. Even so, ARBs are a substitute for ACE inhibitors in those patients who cannot tolerate the latter.
- Activity of ARBs and ACE inhibitors on preload and afterload are similar.
- Their use in HF is mainly as a substitute for ACE inhibitors in those patients with severe cough or angioedema, which are thought to be mediated by elevated bradykinin levels.

Pharmacokinetics

- All the drugs are orally active and are dosed once-daily, with the exception of *valsartan which is* twice a day.
- *Losartan, the prototype of the class, differs* in that it undergoes extensive first-pass hepatic metabolism, including conversion to its active metabolite. The other drugs have inactive metabolites.
- Elimination of metabolites and parent compounds occurs in urine and feces.

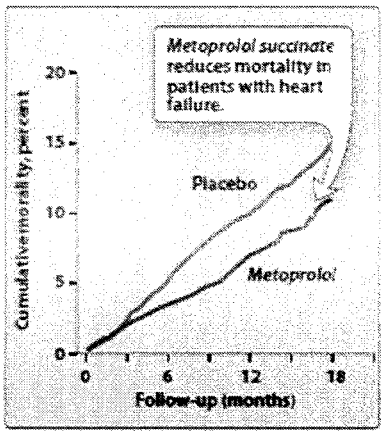
Adverse effects

- ARBs have an adverse effect and drug interaction profile similar to that of ACE inhibitors. However, the ARBs have a lower incidence of cough and angioedema.
- Like ACE inhibitors, ARBs are contraindicated in pregnancy

Aldosterone antagonists

- Patients with advanced heart disease have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone.
- *Spironolactone is a direct antagonist* of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia.
- *Eplerenone is a* competitive antagonist of aldosterone with *a lower incidence of endocrine-related* side effects due to its reduced affinity for glucocorticoid, androgen, and progesterone receptors.
- Aldosterone antagonists are indicated in patients with more severe stages of HFrEF and recent myocardial infarction.

β-BLOCKERS



- β-Blockade is recommended for all patients with chronic, stable HF.
- reduce morbidity and mortality associated with HFrEF.
- Although it may seem counterintuitive to administer drugs with negative inotropic activity in HF, evidence clearly demonstrates improved systolic functioning and reverse cardiac remodeling in patients receiving β-blockers.
- These agents decrease heart rate and inhibit release of renin in the kidneys. In addition, β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.
- Three β-blockers have shown benefit in HF:

  carvedilol (nonselective α , β-adrenoreceptor blocker), *bisoprolol* and long-acting *metoprolol succinate* (β1-adrenoreceptor blocker).
- β-Blockers should also be used with caution with other drugs that slow AV conduction, such as *verapamil, and diltiazem.*

Diuretics

- Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases cardiac workload and oxygen demand.
- Diuretics may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure.
- relieve pulmonary congestion and peripheral edema.
- reducing the symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea.
- Loop diuretics are the most commonly used diuretics in HF. These agents are used for patients who require extensive diuresis and those with renal insufficiency.
- As diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess.

VASO- AND VENODILATORS

- Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance.
- Nitrates are commonly used venous dilators to reduce preload for patients with chronic HF.
- Arterial dilators, such as *hydralazine reduce systemic arteriolar resistance* and decrease afterload.
- If the patient is intolerant of ACE inhibitors or β-blockers, or if additional vasodilator response is required, a combination of *hydralazine and isosorbide dinitrate* may be used.
- A fixed-dose combination of these agents has been shown to improve symptoms and survival in black patients with HFrEF on standard HF treatment (β-blocker plus ACE inhibitor or ARB).
- Headache, hypotension, and tachycardia are common adverse effects with this combination.

INOTROPIC DRUGS

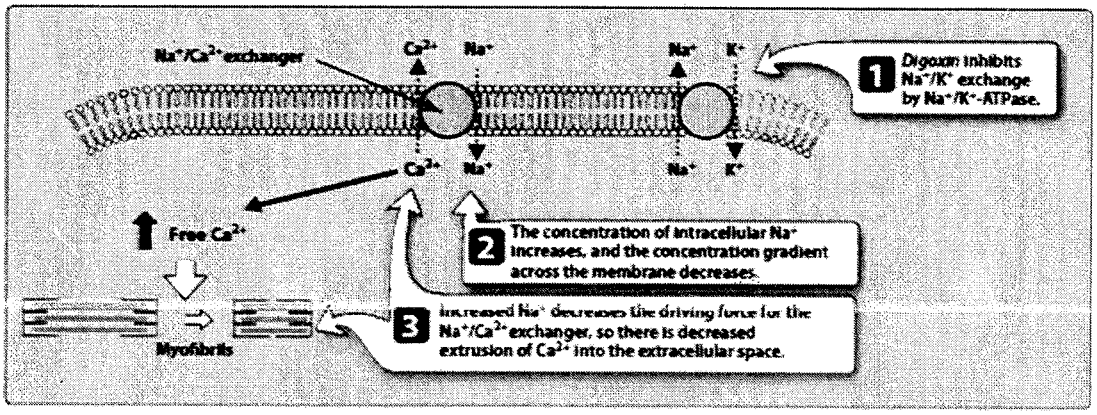
- Positive inotropic agents enhance cardiac contractility and, thus, increase cardiac output.
- act by different mechanisms, the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.
- All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival, especially in patients with HFrEF due to coronary artery disease. For this reason, these agents, with the exception of *digoxin, are only used for a short period mainly in* the inpatient setting.

- **1) Digitalis glycosides**

- often called digitalis or digitalis glycosides, because most of the drugs come from the digitalis (foxglove) plant.
- They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are used in treating HF.
- The digitalis glycosides have a low therapeutic index, with only a small difference between a therapeutic dose and doses that are toxic or even fatal.
- The most widely used agent is *digoxin*. *Digitoxin is seldom used due to its considerable* duration of action.

1) Digitalis glycosides

Mechanism of action



Therapeutic uses:

- *Digoxin* therapy is indicated in patients with severe HFrEF after initiation of ACE inhibitor, β-blocker, and diuretic therapy.
- A low serum drug concentration of *digoxin* (0.5 to 0.8 ng/mL) is beneficial in HFrEF. At this level, patients may see a reduction in HF admissions, along with improved survival.
- At higher serum drug concentrations, admissions are prevented, but mortality likely increases.
- Patients with mild to moderate HF often respond to treatment with ACE inhibitors, β-blockers, aldosterone antagonists, direct vaso- and venodilators, and diuretics and may not require *digoxin*.

Pharmacokinetics:

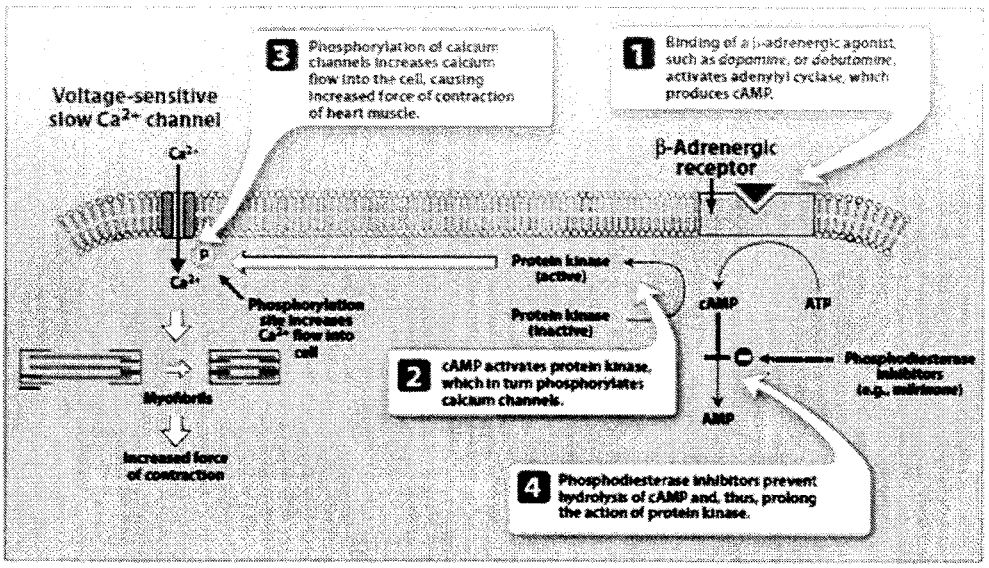
- *Digoxin* is available in oral and injectable formulations.
- It has a large volume of distribution, because it accumulates in muscle.
- In acute situations such as symptomatic atrial fibrillation, a loading dose regimen is used.
- *Digoxin* has a long half-life of 30 to 40 hours.
- It is mainly eliminated intact by the kidney, requiring dose adjustment in renal dysfunction

Adverse effects:

- At low serum drug concentrations, *digoxin* is fairly well tolerated.
- However, it has a very narrow therapeutic index, and *digoxin* toxicity is one of the most common adverse drug reactions leading to hospitalization.
- Anorexia, nausea, and vomiting may be initial indicators of toxicity.
- Patients may also experience blurred vision, yellowish vision (xanthopsia), and various cardiac arrhythmias.
- Toxicity can often be managed by discontinuing *digoxin*, determining serum potassium levels, and, if indicated, replenishing potassium.
- Decreased levels of serum potassium (hypokalemia) predispose a patient to *digoxin* toxicity, since *digoxin* normally competes with potassium for the same binding site on the Na+/K+-ATPase pump.
- With the use of a lower serum drug concentration in HFrEF, toxic levels are infrequent.
- *Digoxin* should also be used with caution with other drugs that slow AV conduction, such as β-blockers, *verapamil*, and *diltiazem*.

2) β-Adrenergic agonists

- β-Adrenergic agonists, such as *dobutamine* and *dopamine*, improve cardiac performance by causing positive inotropic effects and vasodilation.
- *Dobutamine* is the most commonly used inotropic agent other than *digoxin*.
- β-Adrenergic agonists lead to an increase in intracellular cyclic adenosine monophosphate (cAMP), which results in the activation of protein kinase. Protein kinase then phosphorylates slow calcium channels, thereby increasing entry of calcium ions into the myocardial cells and enhancing contraction.
- Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute HF in the hospital setting.



3) Phosphodiesterase inhibitors

- *Milrinone* is a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP. Like β-adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility.
- Long-term, *milrinone* therapy may be associated with a substantial increased risk of mortality.
- However, short-term use of intravenous *milrinone* is not associated with increased mortality in patients without a history of coronary artery disease.

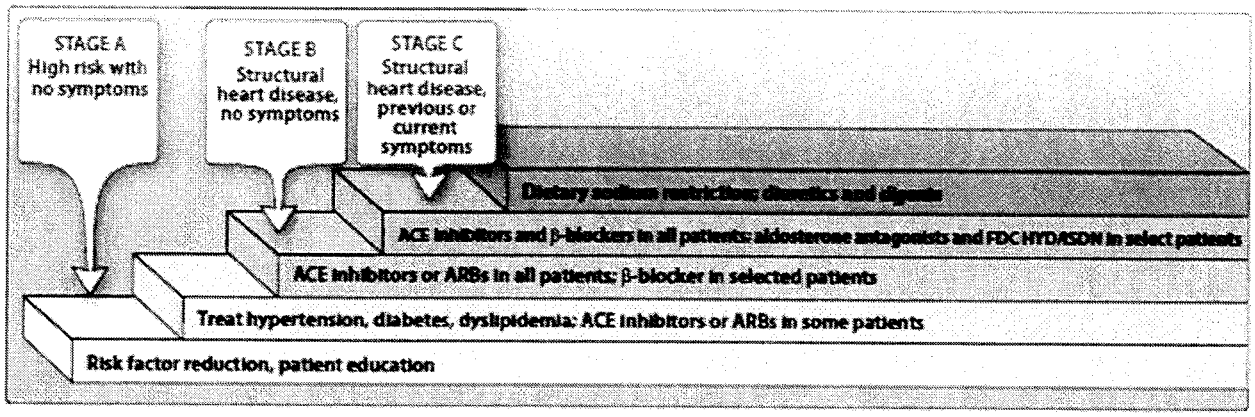
Classification of heart failure

- Class I: No limitation of physical activity
- Class II: Slight limitation of physical activity
- Class III: Marked limitation of physical activity
- Class IV: Unable to carry out physical activity without discomfort

New classification of heart failure

- Stage A: Asymptomatic with no heart damage but have risk factors for heart failure
- Stage B: Asymptomatic but have signs of structural heart damage
- Stage C: Have symptoms and heart damage
- Stage D: End stage disease

ORDER OF THERAPY



ORDER OF THERAPY

- As the disease progresses, polytherapy is initiated.
- In patients with overt HF, loop diuretics are often introduced first for relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema.
- ACE inhibitors or ARBs (if ACE inhibitors are not tolerated) are added after the optimization of diuretic therapy. The dosage is gradually titrated to that which is maximally tolerated and/or produces optimal cardiac output.
- most patients newly diagnosed with HFrEF are initiated on both low doses of an ACE inhibitor and β-blocker after initial stabilization.
- *Digoxin*, aldosterone antagonists, and fixed-dose *hydralazine* and *isosorbide dinitrate* are initiated in patients who continue to have HF symptoms despite optimal doses of an ACE inhibitor and β-blocker.