Drug Therapy of Heart Failure

Munir Gharraibeh, MD, PhD, MHPE
Faculty of Medicine,
The University of Jordan
November, 2014
Drug Therapy of Heart Failure

Definition of Heart Failure

Causes

Classifications
Definition of Heart Failure

• Heart is unable to provide adequate perfusion of peripheral organs to meet their metabolic requirements

• Characterized by:
  1. Decreased CO
  2. Increased TPR

• Progression to congestive heart failure (CHF) is accompanied by peripheral and pulmonary edema.
CAUSES OF CONGESTIVE HEART FAILURE

A. Mechanical Causes
   1. Pressure Overload
      a. Hypertension
      b. Aortic Valve Stenosis
      c. Pulmonary Hypertension
   2. Volume Overload
      a. Valvular Regurgitation
      b. Shunts
      c. Increased Blood Volume

B. Impaired Cardiac Filling
   1. Pericardial Disease (constriction or tamponade)
   2. Restrictive Heart Disease (endo- or myocardial)
   3. Ventricular Hypertrophy
   4. Ventricular Aneurysm

C. Myocardial Failure
   1. Primary
      a. Loss of functioning muscle (myocardial infarction)
      b. Cardiomyopathy
      c. Myocarditis
   2. Secondary
      a. Dysdynamic heart failure (response to chronic overload)
      b. Drug-induced
      c. Involvement in systemic disease (hypothyroidism)
Myofibril syncitium

$\text{Na}^+ - \text{K}^+ \text{ATPase}$

$\text{Ca}^{2+}$

$\text{Ca}^{2+}$-channel blockers

$\beta$ agonists

$\text{Ca}^{2+}$-sensitizers

Actin – tropomyosin – troponin

Sarcomere

Digoxin
Mechanisms of H. F.

Reduction in the intrinsic myocardial contractility

1. Depletion of NE in heart muscle.
3. ATP and other high energy phosphate compounds.
4. $\beta$ receptor density (due to down regulation after chronic exposure to high circulating catecholamines).
5. Abnormal Ca$^{++}$ binding:
   1. Less stored in SR
   2. More stored in Mitochondria
   3. Less released
   4. Lesser reuptake into SR.
   5. Slow reuptake into mitochondria leading to slow relaxation.
Compensatory Mechanisms in Heart Failure

- **Frank Starling Mechanism**
- **Increased Activity of SNS:**
  - a- Tachycardia and increased CO.
  - b- Increased myocardial contractility
  - c- Vasoconstriction leading to redistribution of blood to important viscera
  - d- Renin release leading to increased plasma volume
- **Myocardial Hypertrophy** leading to increased wall tension.
Compensatory SNS Mechanisms in HF

• In a failing heart, the loss of contractile function leads to a decline in CO and a decrease in arterial BP.

• Baroreceptors sense the hemodynamic changes and initiate countermeasures to maintain support of the circulatory system. This is achieved by activation of the SNS.

• This helps maintain adequate cardiac output by:
  1. Increasing myocardial contractility and heart rate ($\beta_1$-adrenergic receptors)
  2. Increasing vasomotor tone ($\alpha_1$-adrenergic receptors) to maintain systemic blood pressure
Consequences of hyperadrenergic state

• Enhancement of RAAS.

• Over the long term, hyperadrenergic state leads to irreversible myocyte damage, cell death, and fibrosis.

• In addition, the augmentation in peripheral vasomotor tone increases LV afterload.

• This places an added stress upon the left ventricle and an increase in myocardial $O_2$ demand (ventricular remodeling).

• The frequency and severity of cardiac arrhythmias are enhanced in the failing heart.
Angiotensin II also facilitates NE release.
Signs and Symptoms of HF

- Tachycardia, sweating
- Decreased exercise tolerance & SOB
- Peripheral and pulmonary edema
- Cardiomegaly
Normal heart

Dilated (congestive) heart

Hypertrophic heart
Factors that May Precipitate Acute Decompensation in Patients with Chronic Heart Failure

- Dietary indiscretion
- Myocardial ischemia/infarction
- Arrhythmias (tachycardia or bradycardia)
- Discontinuation of HF therapy
- Infection
- Anemia
- Initiation of medications that worsen HF:
  - Calcium antagonists (verapamil, diltiazem)
  - Beta blockers
  - Nonsteroidal anti-inflammatory drugs
  - Antiarrhythmic agents [all class I agents, sotalol (class III)]
  - Anti-TNF antibodies
- Alcohol consumption
- Pregnancy
- Worsening hypertension
- Acute valvular insufficiency
Objectives of Long Term Management of Chronic Cardiac Failure

- Improve cardiac performance (hemodynamics) at rest and during exercise.
- Relieve symptoms.
- Improve myocardial efficiency.
- Improve quality of life (particularly symptom-free and effort tolerance).
- Improve patient survival.
Cardiac vs Noncardiac Therapeutic Targets

• Conventional belief that the primary defect in HF is in the heart.
• Reality is that HF involves many other processes and organs.
• Research has shown that therapy directed at noncardiac targets is more valuable than cardiac targets.
• CHF should be viewed as a complex, interrelated sequence of events involving hemodynamic, and neurohormonal events.
Therapeutic Overview

The Problems

• Reduced force of contraction
• Decreased cardiac output
• Increased total peripheral resistance
• Inadequate organ perfusion
• Edema
• Decreased exercise tolerance
• Ischemic heart disease
• Sudden death
• Ventricular remodeling and decreased function
Nonpharmacologic Treatment:

- Salt Restriction
- Treat the Cause
- Moderate Exercise
- Heart Transplantation
Drug Groups Commonly Used in Heart Failure.

Diuretics

Aldosterone receptor antagonists

Angiotensin-converting enzyme inhibitors

Angiotensin receptor blockers

Beta blockers

Cardiac glycosides

Vasodilators

Beta agonists

Bipyridines

Natriuretic peptide
Diuretics

Only for congestive symptoms:

Do not C.O...... may Co

Can be used alone initially ..........IV

May be used in combination with digitalis or others.

Cause K+ Loss, BP,......etc.

Can be reduced or withdrawn
Causes of Diuretic Resistance in Heart Failure

*Noncompliance with medical regimen; excess dietary Na\(^+\) intake

*Decreased renal perfusion and glomerular filtration rate

*Selective reduction in glomerular perfusion pressure following initiation (or dose increase) of ACE inhibitor therapy

*Nonsteroidal antiinflammatory drugs

*Primary renal pathology

*Reduced or impaired diuretic absorption due to gut wall edema and reduced splanchnic blood flow
Angiotensin Converting Enzyme Inhibitors "ACEI"

- **Pharmacological Actions:**
  - Reduce angiotensin II levels.
  - Increase bradykinin.
  - Inhibit SNS, leading to decreased NE release and upregulation of $\beta_1$ receptors.
  - Balanced vasodilators.
  - Reduce myocyte & fibroblast growth factors.
  - Reduce salt and water retention.
  - Reduce K+ loss.
  - Reduce ventricular arrhythmias.

Munir Gharaibeh, MD, PhD, MHPE
Effects of AT-II

- Decreased cardiac function
- Decreased renal perfusion
- Vasoconstriction
- Sodium depletion (diuretics)

**Plasma Angiotensinogen**

**Renin**

**Plasma Angiotensin I**

**Plasma Angiotensin II**

**AT1 Receptor**

<table>
<thead>
<tr>
<th>Sympathetic activation</th>
<th>Vasoconstriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone release</td>
<td>Sodium retention</td>
</tr>
<tr>
<td>Myocyte hypertrophy</td>
<td>Myocardial and</td>
</tr>
<tr>
<td>Myocardial fibrosis</td>
<td>vascular fibrosis</td>
</tr>
<tr>
<td>Myocyte apoptosis</td>
<td>Endothelin synthesis</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>Cytokine release</td>
</tr>
<tr>
<td>Altered gene expression</td>
<td></td>
</tr>
</tbody>
</table>

**ACE**
# Potential Roles of Aldosterone in the Pathophysiology of Heart Failure

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>PATHOPHYSIOLOGICAL EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Na(^+) and water retention</td>
<td>Edema, elevated cardiac filling pressures</td>
</tr>
<tr>
<td>K(^+) and Mg(^{2+}) loss</td>
<td>Arrhythmogenesis and risk of sudden cardiac death</td>
</tr>
<tr>
<td>Reduced myocardial norepinephrine uptake</td>
<td>Potentiation of norepinephrine effects: myocardial remodeling and arrhythmogenesis</td>
</tr>
<tr>
<td>Reduced baroreceptor sensitivity</td>
<td>Reduced parasympathetic activity and risk of sudden cardiac death</td>
</tr>
<tr>
<td>Myocardial fibrosis, fibroblast proliferation</td>
<td>Remodeling and ventricular dysfunction</td>
</tr>
<tr>
<td>Alterations in Na(^+) channel expression</td>
<td>Increased excitability and contractility of cardiac myocytes</td>
</tr>
</tbody>
</table>

Munir Gharibeh, MD, PhD, MHPE
Therapeutic Actions of ACEI

- Blockade of ACE
- Decreased AT-II
- Decreased aldosterone
- Decreased fluid retention
- Vasodilation
- Reduced preload and afterload
- Slowing of cardiac remodeling
Therapeutic Values of ACEI

- Nowadays drugs of choice.
- No tolerance.
- Retard progression of HF.
- Decrease arrhythmias.
- The only drugs which decrease mortality, but only when the highest tolerated doses are used.
Preparations of ACEI

- Captopril
- Enalapril
- Lisinopril
- Quinapril
- Fosinopril

All are similarly effective
Might differ in toxicity
Toxicity of ACEI

- Hypotension .......... First dose phenomenon
- Renal Impairment ............. Proteinurea
- K+ retention
- Cough
Angiotensin (AT1) Receptor Blockers

ARBs

- Losartan.
- Candesartan.
- Valsartan.
- Irbesartan (Approvel).
- Telmisartan (Micardis).

Not superior to ACEIs, but may be useful for patients who cannot tolerate ACEIs because of cough.

Munir Gharaiabeh, MD, PhD, MHPE
Beta Blockers

• Traditionally, they have negative inotropic effects.
• However, nowadays there is overwhelming evidence to support the use of β-blockers in CHF.
• Not useful in refractory HF.
• Mechanism involved remains unclear.
• Part of their beneficial effects may derive from slowing of heart rate, decreased cardiac work and consequently decreased myocardial O₂ consumption and enhanced efficiency.
• This would lessen the frequency of ischemic events and arrhythmias.
Beta blockers

- Suggested mechanisms also include reduced remodeling of the heart muscle.
- $\beta$-Blockers may be beneficial through resensitization of the down-regulated receptor, thus improving myocardial contractility.
- Should be started with low doses and gradually increased.
- Recent studies with metoprolol, carvedilol, bicindolol, and bisiprolol showed a reduction in mortality in patients with these drugs.
- This does not mean that other older agents are not effective.
- Contraindicated in severe, refractory, unstable cases.

Munir Gharaibeh, MD, PhD, MHPE

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
*p < .005 vs. placebo
**p < .0001 vs. placebo

Δ LVEF (EF units)

Placebo | 6.25 mg bid | 12.5 mg bid | 25 mg bid

Carvedilol


Copyright © The McGraw-Hill Companies, Inc., all rights reserved.
Positive Inotropic Agents

- Logically will improve cardiac function.
- These drugs increase force of contraction by increasing intracellular cardiac Ca$^{++}$ concentration.

- **Cyclic AMP Independent Agents:**
  - Digitalis
  - Pimobendan

- **Cyclic AMP Dependant Agents:**
  - β-adrenergic Agonists
  - Phosphodiesterase Inhibitors
Role of Calcium and Sodium in Myocardial contraction

1. **Ca**\(^{++}\) entry from outside the cell triggers the release of a much larger quantity of **Ca**\(^{++}\) from the sarcoplasmic reticulum.

2. Increased **Ca**\(^{++}\) concentration initiates the contractile process.

3. **Ca**\(^{++}\) is removed by re-uptake into the sarcoplasmic reticulum and by extrusion from the cell by a **Ca**\(^{++}/Na**\(^{+}\) exchange.

4. Sodium balance is restored by **Na**\(^{+}/K**\(^{+}\) ATPase.

Voltage-sensitive slow **Ca**\(^{++}\) channel

**Na**\(^{+}/Ca**\(^{++}\) Exchange

**Na**\(^{+}/K**\(^{+}\) ATPase

**Ca**\(^{++}\) stores (Sarcoplasmic reticulum)

↑ free **Ca**\(^{++}\)

Myofibrils

Munir Sharabi, MD, PhD, MHPE
Action potential (AP) depolarises plasma membrane

NA acts on β₁-adrenoceptors, resulting in phosphorylation of Ca²⁺ channel, which increases channel open times

Mechanisms involved in the increase in [Ca²⁺]:

(i) Depolarisation allows Ca²⁺ influx through voltage-gated Ca²⁺ channels

(ii) Ca²⁺-activated Ca²⁺ release from sarcoplasmic reticulum (SR) increases [Ca²⁺] still further

Mechanisms involved in the decrease in [Ca²⁺]:

(i) Ca²⁺ is extruded in exchange for Na⁺ by Ca²⁺ exchanger (CE)

(ii) Na⁺ is exchanged with K⁺ by the Na⁺/K⁺ ATPase (sodium pump; SP)

Calcium interacts with troponin C, causing contraction

Cardiac glycosides inhibit the sodium pump, leading to:
- [Na⁺]i, which decreases transmembrane Na⁺ gradient and slows extrusion of Ca²⁺ by CE; this leads to:
  - [Ca²⁺]i which leads to:
    - force of contraction

- Milrinone. Rarely used.
The inhibition of PDE III causes ↑cAMP, ↑PKA activation, ↑phosphorylation of Ca²⁺ channels

Dobutamine, xamoterol ↑force of contraction, less ↑of rate than with sympathetic action
Positive Inotropic Agents

Cyclic AMP Independent Agents:

- **Digitalis**: inhibits Na/KATPase.
- **Pimobendan**: sensitizes myocytes to Ca$^{++}$, also inhibits PDE.
Digitalis Glycosides

History:

• Egyptians ------- Squill (العنصل)
• Chinese -------- Toad skin
• William Withering ------ Foxglove 1785

• Digitalis purpura
• Digitalis lanata
• Strophanthus
Digitalis Glycosides

Mechanism:

- Inhibition of Na+/K+ ATPase
Digitalis inhibits Na⁺-K⁺ exchange by Na⁺-K⁺-ATPase.

1. Concentration of intracellular Na⁺ increases.
2. Increased Na⁺ leads to a greater Ca⁺⁺ influx, causing stronger systolic contraction.

Ca⁺⁺ stores (Sarcoplasmic reticulum)

Ca⁺⁺ stores

Na⁺-K⁺-ATPase

K⁺

Na⁺

Ca⁺⁺

Na⁺

K⁺

Ca⁺⁺

Myofibrils

Munir Gharibeh, MD, PhD, MHPE
Digitalis Glycosides

Actions:

- Positive Inotropic Effect
- Vascular Muscle Contraction
- Vagal Stimulation
- Effects on Electrical Properties of Cardiac Tissues.
lactone ring

steroid nucleus

sugar residues

Source: Brunton LL, Lazo JS, Parker KL: Goodman & Gilman’s The Pharmacological Basis of Therapeutics, 11th Edition; http://www.accessmedicine.com

Munir Gharaibeh, MD, PhD, MHPE

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
Digitalis

Contractility
(Heart and Vascular Muscle)

Normal
- C.O
- PVR

Failure
- C.O
- PVR

Munir Gharaibeh, MD, PhD, MHPE
## Effects of Digoxin on Electrical Properties of Cardiac Tissues.

<table>
<thead>
<tr>
<th>Tissue or Variable</th>
<th>Effects at Therapeutic Dosage</th>
<th>Effects at Toxic Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus node</td>
<td>↓ Rate</td>
<td>↓ Rate</td>
</tr>
<tr>
<td>Atrial muscle</td>
<td>↓ Refractory period</td>
<td>↓ Refractory period, arrhythmias</td>
</tr>
<tr>
<td>Atrioventricular node</td>
<td>↓ Conduction velocity, ↑ refractory period</td>
<td>↓ Refractory period, arrhythmias</td>
</tr>
<tr>
<td>Purkinje system, ventricular muscle</td>
<td>Slight ↓ refractory period</td>
<td>Extrasystoles, tachycardia, fibrillation</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>↑ PR interval, QT interval</td>
<td>Tachycardia, fibrillation, arrest at extremely high dosage</td>
</tr>
</tbody>
</table>

Munir Gharabeh, MD, PhD, MHPE
Digitalis Toxicity

- **G.I.T.** (Anorexia, nausea, intestinal cramping, diarrhea)
- **Visual** (Xanthopsia, abnormalities in color vision)
- **Neurologic** (Malaise, confusion, depression, vertigo)
- **Cardiac** (bradycardia, Palpitations, syncope, arrhythmias, AV node block, ventricular tachycardia).

**Interactions.**

*Pharmacological and toxic effects are greater in hypokalemic patients.*

*K⁺*-depleting diuretics are a major contributing factor to digoxin toxicity.
Digitalis Toxicity

Treatment of Toxicity:
Reduce or stop the drug.
Cardiac pacemaker for heart block.
Digitalis antibodies (Digoxin Immune Fab).
Arrhythmias may be converted to normal sinus rhythm by $K^+$ when the plasma $K^+$ conc. is low or within the normal range.
When the plasma $K^+$ conc is high, antiarrhythmic drugs, such as lidocaine, phenytoin, procainamide, or propranolol, can be used.

Munir Ghrabein, MD, PhD, MHPE
Digitalis Glycosides

Therapeutic Benefits:

• Nowadays, *only useful in CCHF with supraventricular arrhythmia*
  – Might decrease morbidity
  – ? Withdrawal
  – ? Mortality
## Basic Data of Three Cardiac Glycosides

<table>
<thead>
<tr>
<th></th>
<th>Digitoxin</th>
<th>Digoxin</th>
<th>Ouabain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI absorption</strong></td>
<td>100%</td>
<td>70–85%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Polarity</strong></td>
<td>Least</td>
<td>Somewhat</td>
<td>Highest</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>97%</td>
<td>&lt;30%</td>
<td>5–10%</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>4–7 days</td>
<td>1.5-1.6 days</td>
<td>21 hr</td>
</tr>
<tr>
<td><strong>Excretion route</strong></td>
<td>Stool and kidneys; as hepatic metabolites*</td>
<td>Kidneys; largely unchanged</td>
<td>Kidneys; largely unchanged</td>
</tr>
<tr>
<td><strong>Enterohepatic recycling</strong></td>
<td>27%</td>
<td>6.8%</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Optimum serum levels</strong></td>
<td>20-35 ng/ml</td>
<td>0.5-2.5 ng/ml</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>V_d</strong></td>
<td>0.6 L/kg</td>
<td>5-10 L/kg</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* About 8% of digitoxin is metabolized and excreted as digoxin in the urine. Digitoxin seems to be largely recycled to complete its metabolic degradation.
Positive Inotropic Agents

Cyclic AMP Dependent Agents:

β-adrenergic Agonists:

- NE
- Dopamine
- Dobutamine

Phosphodiesterase Inhibitors:

- Amrinone
- Inamrinone
- Milrinone
- Vesanirone
- Sildenafil
Positive Inotropic Agents

Cyclic AMP Dependent Agents: 

β-adrenergic Agonists:

All increase myocardial oxygen consumption, so not helpful for chronic use, maybe used (IV) for short term or in acute heart failure.

NE:
Was used in cardiogenic shock, but caused severe vasospasm and gangrene.

Ep:
Still used in cardiac arrest, by intracardiac injection.
Positive Inotropic Agents

**Dopamine:**

Widely used in cardiogenic shock.

**Low doses:** stimulate DA_1 receptors leading to renal vasodilation and improved renal function.

**Intermediate doses:** work on β_1 receptors leading to positive inotropic actions.

**High doses:** stimulate α receptors leading to vasoconstriction and elevation of blood pressure. Can cause arrhythmias and ischemic changes.

**Dobutamine:**

Selective β_1 agonist, used intermittently (IV) in CCHF. Produces mild vasodilation.

Has more inotropic than chronotropic actions.
**Voltage sensitive slow Ca^{++} channel**

1. Binding of β-adrenergic agonist (such as, dopamine, dobutamine) activates adenylyl cyclase, which produces cAMP.

2. cAMP activates protein kinase, which in turn phosphorylates a calcium channel.

3. Phosphorylation of calcium channel increases calcium flow into cell causing increased force of contraction of heart muscle.

4. Phosphodiesterase inhibitors prevent hydrolysis of cAMP and thus prolong action of protein kinase.

**Figure 16.11**
Sites of action of β-adrenergic agonists on heart muscle.
Positive Inotropic Agents

Phosphodiesterase Inhibitors:

PDE inhibition leads to accumulation of cAMP and cGMP leading to positive inotropic activity and peripheral vasodilation.

Toxic: arrhythmias, and thrombocytopenia.

Short acting, so reserved for parenteral therapy of acute heart failure.

- Inamrinone (PDE-3)
- Milrinone (PDE-3)
- Vesanirone (PDE-3)
- Sildenafil (PDE-5)
Vasodilators

• Affect preload and/or afterload without directly affecting contractility.
• Consequently can decrease myocardial ischemia, enhance coronary blood flow and decrease MVO2.
• Can be used in acute heart failure and for short periods in CCHF.
• Hydralazine-Isosorbide dinitrate combination was found to decrease mortality, maybe by reducing remodeling of the heart.
• Can be combined with ACEI, Diuretics and digitalis.
(BNP)-Niseritide

• Brain (B-type) natriuretic peptide (BNP) is secreted constitutively by ventricular myocytes in response to stretch.

• BNP binds to receptors in the vasculature, kidney, and other organs, producing potent vasodilation with rapid onset and offset of action by increasing levels of cGMP.

• Niseritide is recombinant human BNP approved for treatment of acute decompensated CHF.
(BNP)-Niseritide

- Reduces systemic and pulmonary vascular resistances, causing an indirect increase in cardiac output and diuresis.

- Effective in HF because of reduction in preload and afterload.

- Hypotension is the main side effect.
<table>
<thead>
<tr>
<th>Venous Dilators</th>
<th>Mixed Action</th>
<th>Arterial Dilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Nitroprusside</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Captopril</td>
<td>Minoxidil</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydralazine + Nitrate</td>
<td></td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV</td>
<td>LVEDV</td>
<td>LVEDV</td>
</tr>
<tr>
<td>↓ LVEDV</td>
<td>↓ LVEDV</td>
<td>↓ LVEDV</td>
</tr>
<tr>
<td>↓ MVO2</td>
<td>↓ MVO2</td>
<td>↓ MVO2</td>
</tr>
<tr>
<td>← CO</td>
<td>↑ CO</td>
<td>↑ CO</td>
</tr>
</tbody>
</table>

Munir Gharaibeh, MD, PhD, MHPE
Munir Gharabeh, MD, PhD, MHPE
# Vasodilator Drugs Used to Treat Heart Failure

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>EXAMPLES</th>
<th>MECHANISM OF VASODILATING ACTION</th>
<th>PRELOAD REDUCTION</th>
<th>AFTERLOAD REDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic nitrates</td>
<td>Nitroglycerin, isosorbide dinitrate</td>
<td>NO-mediated vasodilation</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Nitric oxide donors</td>
<td>Nitroprusside</td>
<td>NO-mediated vasodilation</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Captopril, enalapril, lisinopril</td>
<td>Inhibition of Ang II generation, decreased bradykinin degradation</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Losartan, candesartan</td>
<td>Blockade of AT&lt;sub&gt;1&lt;/sub&gt; receptors</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors</td>
<td>Milrinone, inamrinone</td>
<td>Inhibition of cyclic AMP degradation</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Direct-acting K&lt;sup&gt;+&lt;/sup&gt;-channel agonist</td>
<td>Hydralazine</td>
<td>Unknown</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>α-adrenergic antagonists</td>
<td>Doxazosin, prazosin</td>
<td>Selective α&lt;sub&gt;1&lt;/sub&gt; adrenergic receptor blockade</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Nonselective α-adrenergic antagonists</td>
<td>Phentolamine</td>
<td>Nonselective adrenergic receptor blockade</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Vasodilating β&lt;sub&gt;1&lt;/sub&gt;-adrenergic antagonists</td>
<td>Carvedilol, labetalol</td>
<td>Selective β&lt;sub&gt;1&lt;/sub&gt; adrenergic receptor blockade</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt; channel blockers</td>
<td>Amlodipine, nifedipine, felodipine</td>
<td>Inhibition of L-type Ca&lt;sup&gt;2+&lt;/sup&gt; channels</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>β-adrenergic agonists</td>
<td>Isoproterenol</td>
<td>Stimulation of vascular β&lt;sub&gt;2&lt;/sub&gt; adrenergic receptors</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Reduced Cardiac Output

Inotropes

Venodilators
Fluid retention
Increased preload

Arteriolar vasodilators

Peripheral vasoconstriction
Stage A
High risk with no symptoms

Stage B
Structural heart disease, no symptoms

Stage C
Structural disease, previous or current symptoms

Stage D
Refractory symptoms requiring special intervention

Hospice
VAD; transplantation
Inotropes
Aldosterone antagonist, nesinitide
Consider multidisciplinary team
Revascularization, mitral-valve surgery
Cardiac resynchronization if bundle-branch block present
Dietary Na+ restriction, diuretics, and digoxin
ACE inhibitors and β blockers in all patients
ACE inhibitors or AT₁ blockers in all patients; β blockers in selected patients
Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or AT₁ blockers in some patients
Risk-factor reduction, patient and family education


Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
# Steps in the Prevention and Treatment of Chronic Heart Failure.

<table>
<thead>
<tr>
<th>ACC/AHA Stage</th>
<th>Step&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, B</td>
<td>1</td>
<td>Control hypertension, hyperlipidemia, glucose metabolism (diabetes), obesity</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>Reduce workload of the heart (limit activity, put on temporary bed rest)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Restrict sodium intake, give diuretics</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Restrict water (rarely required)</td>
</tr>
<tr>
<td>C, D</td>
<td>5</td>
<td>Give angiotensin-converting enzyme inhibitor or angiotensin receptor blocker</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Give digitalis if systolic dysfunction with third heart sound or atrial fibrillation is present</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Give β blockers to patients with stable class II–IV heart failure</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Give aldosterone antagonist</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Give vasodilators</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>Cardiac resynchronization if wide QRS interval is present in normal sinus rhythm</td>
</tr>
</tbody>
</table>

<sup>1</sup> Munir Gharaibeh, MD, PhD, MHPE
Errors in Management of HF

- Missed diagnosis.
- Improper dosage of diuretics.
- Failure to assess quality of life.
- Failure to consider long term therapeutic goals.
- Underprescribing of ACEI.
- Use of potentially harmful drugs.
- Failure to use hydralazine-isosorbide combination which has proved evidence of benefit.

Munir Gheraibeh, MD, PhD, MHPE
مفهوم لو اعيدلكم الدرس ....