Chronic Heart Failure
REFERENCES


- Pharmacotherapy; a pathophysiologic approach (Dipiro 8th edition, 2011)

### CLASS I
**Benefit >> Risk**
- Procedure/Treatment SHOULD be performed/administered

### CLASS IIa
**Benefit >> Risk**
- Additional studies with focused objectives needed
- IT IS REASONABLE to perform procedure/administer treatment

### CLASS IIb
**Benefit ≥ Risk**
- Additional studies with broad objectives needed; additional registry data would be helpful
- Procedure/Treatment MAY BE CONSIDERED

### CLASS III or CLASS III Harm
- Procedure/Test
- Treatment
  - COR III: No benefit
  - COR III: Excess Cost w/o Benefit or Harmful
  - COR III: Harmful to Patients

#### LEVEL A
- Multiple populations evaluated*
- Data derived from multiple randomized clinical trials or meta-analyses
- Recommendation that procedure or treatment is useful/effective
- Sufficient evidence from multiple randomized trials or meta-analyses

#### LEVEL B
- Limited populations evaluated*
- Data derived from a single randomized trial or nonrandomized studies
- Recommendation that procedure or treatment is useful/effective
- Evidence from single randomized trial or nonrandomized studies

#### LEVEL C
- Very limited populations evaluated*
- Only consensus opinion of experts, case studies, or standard of care
- Recommendation that procedure or treatment is useful/effective
- Only expert opinion, case studies, or standard of care

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**Suggested phrases for writing recommendations**
- should
- is recommended
- is indicated
- is useful/effective/beneficial
- can be useful/effective/beneficial
- is probably recommended
- or indicated

**Comparative effectiveness phrases**
- treatment/strategy A is recommended/indicated in preference to treatment B
- treatment A should be chosen over treatment B
- treatment/strategy A is probably recommended/indicated in preference to treatment B
- it is reasonable to choose treatment A over treatment B
- may/might be considered
- may/might be reasonable
- usefulness/effectiveness is unknown/unclear/uncertain or not well established
- COR III: No Benefit
- COR III: Potentially harmful
- COR III: Harm associated with excess morbidity/mortality
- COR III: Should not be performed/administered/other

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*Note: * indicates additional considerations for specific circumstances.
• We will focus on treatment of patients with systolic dysfunction (with or without concurrent diastolic dysfunction)
HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema.

Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema, dyspnea, or fatigue. Because some patients present without signs or symptoms of volume overload, the term “heart failure” is preferred over “congestive heart failure.” There is no single diagnostic test for HF because it is largely a clinical diagnosis based on a careful history and physical examination.
The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels or from certain metabolic abnormalities, but most patients with HF have symptoms due to impaired left ventricular (LV) myocardial function. It should be emphasized that HF is not synonymous with either cardiomyopathy or LV dysfunction; these latter terms describe possible structural or functional reasons for the development of HF.
• The definition of heart failure with reduced ejection fraction (HFrEF) has varied, with guidelines of left ventricular ejection fraction (LVEF) ≤35%, <40%, and ≤40%.

• According to the AHA/ACC, HFrEF is defined as the clinical diagnosis of HF and EF ≤40%.

• The term heart failure with preserved ejection fraction (HFpEF) has been variably classified as EF >40%, >45%, >50%, and ≥55%. Because some of these patients do not have entirely normal EF but also do not have major reduction in systolic function, the term preserved EF has been used. Patients with an EF in the range of 40% to 50% represent an intermediate group.
<table>
<thead>
<tr>
<th>Classification</th>
<th>EF (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Heart failure with reduced ejection fraction (HFrEF)</td>
<td>≤40</td>
<td>Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>II. Heart failure with preserved ejection fraction (HFpEF)</td>
<td>≥50</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFpEF, borderline</td>
<td>41 to 49</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.</td>
</tr>
<tr>
<td>b. HFpEF, improved</td>
<td>&gt;40</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.
Epidemiology

- The lifetime risk of developing HF is 20% for Americans ≥40 years of age. In the United States, HF incidence has largely remained stable over the past several decades, with >650,000 new HF cases diagnosed annually. In 2012, HF costs in the United States exceeded $40 billion.

- 75% of HF cases have history of hypertension
  - aggressive treatment of hypertension may have contributed to the lower incidence of HF in some populations

- 22% of males and 46% of females are disabled with heart failure within 6 years of myocardial infarction
  - improved survival after myocardial infarction (MI) may leave patients at greater risk of developing post-infarction HF

- Incidence x 2 in last ten years

- Heart failure is more common in men than in women until age 65 years.

- HF incidence approaches 10 per 1000 population after 65 years of age.
  - as the size of the geriatric population increases, HF likely will become a more frequently encountered clinical entity

Gottdiener J et al. JACC 2000;35:1628
Haldeman GA et al. Am Heart J 1999;137:352
Prognosis

- Despite earlier diagnosis and aggressive medical management of HF, the **prognosis is poor**.
- **Factors affecting the prognosis** of patients with heart failure include, but are not limited to, age, gender, LVEF, renal function, blood pressure, heart failure etiology, and drug or device therapy.
- The **quality of life** is adversely affected by progressive functional disability.
- A greater consequence is the **high mortality rate**.
  - 5 year mortality rate is 50% (AHA/ACC 2013)
  - 80% of men and 70% of women under age 65 who have CHF will die within 8 years
  - **Median survival** following onset is 1.7 years for men and 3.2 years for women

Etiologies

• Heart failure can result from any disorder that affects the ability of the heart to contract (systolic function) and/or relax (diastolic dysfunction):
  – Ischemic heart disease, mostly acute myocardial infarction
    • Causes 50-6-% of cases of HF
  – Hypertension
• Suspected primary etiology in 30-40% of patients; history of HTN present in 70-80% of HF patients. Long-term treatment of both systolic and diastolic hypertension reduces the risk of HF by approximately 50%
  – Idiopathic dilated cardiomyopathy
    • Etiology in 5-10% of patients
  – Other cardiomyopathies (e.g. alcoholic, viral, hypertrophic)
  – Drug induced
    • examples
Drugs that may precipitate or exacerbate HF

**TABLE 20-3** Drugs that May Precipitate or Exacerbate Heart Failure

*Negative inotropic effect*
- Antiarrhythmics (e.g., disopyramide, flecainide, and propafenone)
- Beta-blockers (e.g., propranolol, metoprolol, and atenolol)
- Calcium channel blockers (e.g., verapamil and diltiazem)
- Itraconazole
- Terbinafine

*Cardiotoxic*
- Doxorubicin
- Daunomycin
- Cyclophosphamide
- Trastuzumab
- Ethanol
- Amphetamines (e.g., cocaine and methamphetamine)

*Sodium and water retention*
- NSAIDs
- COX-2 inhibitors
- Rosiglitazone and pioglitazone
- Glucocorticoids
- Androgens and estrogens
- Salicylates (high-dose)
- Sodium-containing drugs (e.g., carbenicillin disodium and ticarcillin disodium)
- Imatinib

*Abbreviations:* COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal antiinflammatory drugs.
Descriptive terms in HF

- Low-output versus high-output failure
- Left versus right ventricular heart failure
- Systolic versus diastolic heart failure
- Ischemic versus nonischemic heart failure
- Acute versus chronic heart failure
<table>
<thead>
<tr>
<th>Type of Failure</th>
<th>Characteristics</th>
<th>Contributing Factors</th>
<th>Etiology</th>
</tr>
</thead>
</table>
| Low output, systolic dysfunction     | Hypofunctioning left ventricle; enlarged heart; ↑left ventricular end-diastolic volume; EF <40%; ↓stroke volume; ↓CO; $S_3$ heart sound present | 1. ↓Contractility (cardiomyopathy)  
2. ↑Afterload (elevated SVR)                                                           | 1. Coronary ischemia, MI, mitral valve stenosis or regurgitation, alcoholism, viral syndromes, nutritional deficiency, calcium and potassium depletion, drug induced, idiopathic  
2. Hypertension, aortic stenosis, volume overload                                    |
| dilated cardiomyopathy (60%–70% of cases) |                                                                                |                                                                                      |                                                                                                               |
| Low output, diastolic dysfunction    | Normal left ventricular contractility; normal size heart; stiff left ventricle; impaired left ventricular relaxation; impaired left ventricular filling; ↓left ventricular end-diastolic volume; normal EF; ↓SV; ↓CO; exaggerated $S_4$ heart sound | 1. Thickened left ventricle (hypertrophic cardiomyopathy)  
2. Stiff left ventricle (restrictive cardiomyopathy)  
3. ↑Preload | 1. Coronary ischemia, MI hypertension, aortic stenosis and regurgitation, pericarditis, enlarged left ventricular septum (hypertrophic cardiomyopathy)  
2. Amyloidosis, sarcoidosis  
3. Sodium and water retention                                                      |
| (30%–40% of cases)                   |                                                                                |                                                                                      |                                                                                                               |
| High-output failure                  | Normal or ↑contractility; normal size heart; normal left ventricular end-diastolic volume; normal or ↑EF; normal or increased stroke volume; ↑CO | ↑Metabolic and oxygen demands                                                        | Anemia and hyperthyroidism                                                                                     |
| (uncommon)                           |                                                                                |                                                                                      |                                                                                                               |

CO, cardiac output; EF, ejection fraction; K, potassium; MI, myocardial infarction; SV, stroke volume; SVR, systemic vascular resistance.
Cardiomyopathy – types

Types of Cardiomyopathy

There are three main types of cardiomyopathy—dilated, hypertrophic, and restrictive. In dilated cardiomyopathy, the ventricles enlarge. In hypertrophic cardiomyopathy, the walls of the ventricles thicken and become stiff. In restrictive cardiomyopathy, the walls of the ventricles become stiff, but not necessarily thickened.
Right vs. left HF

- **Note:** Congestion occurs behind the failing ventricle
  - Pulmonary congestion results from left ventricular failure
  - Systemic congestion results from right ventricular failure
<table>
<thead>
<tr>
<th><strong>Right-sided</strong></th>
<th><strong>Left-sided</strong></th>
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</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>Dyspnea on exertion</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>Paroxysmal nocturnal dyspnea</td>
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<tr>
<td>Hepatomegaly</td>
<td>Orthopnea</td>
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<tr>
<td>Abdominal pain</td>
<td>Tachypnea</td>
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<tr>
<td>Anorexia</td>
<td>Cough</td>
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<tr>
<td>Nausea</td>
<td>Bibasilar rales</td>
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<tr>
<td>Bloating</td>
<td>Pulmonary edema</td>
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<tr>
<td>Constipation</td>
<td>S3 gallop</td>
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<tr>
<td>Ascites</td>
<td>Pleural effusion</td>
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<td></td>
<td>Cheyne-Stokes respiration</td>
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<td></td>
<td>Hemoptysis</td>
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<tr>
<td>Systolic vs. diastolic HF</td>
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<td>--------------------------</td>
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<tr>
<td><strong>Systolic dysfunction</strong></td>
<td></td>
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<tr>
<td>– Impaired ejection</td>
<td></td>
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<tr>
<td>– Decreased contractility</td>
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<tr>
<td><strong>S&amp;S</strong></td>
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<tr>
<td>– Low EF (&lt;45%)</td>
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<tr>
<td>– Cardiomegaly</td>
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<tr>
<td>– S3</td>
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<tr>
<td>– Normal wall thickness</td>
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<tr>
<td>– Hypokinesis</td>
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<tr>
<td>– Symptoms primarily those of reduced cardiac output.</td>
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<tr>
<td><strong>Diastolic dysfunction</strong></td>
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<tr>
<td>– Impaired filling</td>
<td></td>
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<tr>
<td>– Depressed relaxation</td>
<td></td>
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<tr>
<td>– Clinical trials lacking</td>
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<tr>
<td>This group of patients</td>
<td></td>
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<tr>
<td><strong>S&amp;S</strong></td>
<td></td>
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<tr>
<td>– Normal to ↑ EF</td>
<td></td>
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<tr>
<td>– Normal size heart</td>
<td></td>
</tr>
<tr>
<td>– S4</td>
<td></td>
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<tr>
<td>– ↑ wall thickness</td>
<td></td>
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<tr>
<td>– Hyperkinesis</td>
<td></td>
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<tr>
<td>– Symptoms primarily those of blood congestion and may include marked dyspnea and fatigue</td>
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</tr>
</tbody>
</table>
Causes of Heart Failure

Systolic dysfunction (decreased contractility)
• Reduction in muscle mass (e.g., myocardial infarction)
• Dilated cardiomyopathies
• Ventricular hypertrophy
  – Pressure overload (e.g., systemic or pulmonary hypertension, aortic or pulmonic valve stenosis)
  – Volume overload (e.g., valvular regurgitation, shunts, high-output states)

Diastolic dysfunction (restriction in ventricular filling) = heart failure with preserved left ventricular function)
• Increased ventricular stiffness
  – Ventricular hypertrophy (e.g., hypertrophic cardiomyopathy, other examples above)
  – Infiltrative myocardial diseases (e.g., amyloidosis, sarcoidosis, endomyocardial fibrosis)
  – Myocardial ischemia and infarction
• Mitral or tricuspid valve stenosis
• Pericardial disease (e.g., pericarditis, pericardial tamponade)
Pathophysiology of HF

• May involve
  – The right ventricle,
  – The left ventricle
  – Or both,

• The majority of patients with HF have symptoms due to an impairment of left ventricular function.

• Regardless of the etiology of heart failure, the underlying pathophysiologic process and principal clinical manifestations (fatigue, dyspnea, and volume overload) are similar and appear to be independent of the initial cause.
Cardiac Workload

• A common factor to all forms of HF is increased cardiac workload.

• The major determinants of left ventricular workload are:
  1. preload,
  2. afterload,
  3. contractility,
  4. heart rate (HR),
  5. myocardial compliance
Refresh Your Memory!

- **Cardiac Output (CO):** The volume of blood pumped by each ventricle each minute
  
  Cardiac Output = heart rate X stroke volume

- **Stroke Volume (SV):** The volume of blood pumped out of each ventricle with each contraction or beat of the heart.
  
  Stroke volume = end-diastolic volume – end-systolic volume

- **Heart rate** is controlled by the autonomic nervous system. Stroke volume, or the volume of blood ejected during systole, depends on **preload**, **afterload**, and **contractility**

- **End-diastolic volume (EDV):** the volume of blood in the ventricle at the end of diastole when filing is complete

- **End-systolic volume (ESV):** the volume of blood in the ventricle at the end of systole when emptying is complete

- **Ejection Fraction (EF):**
  
  \[
  \text{Ejection Fraction (EF)} = \frac{\text{Stroke Volume}}{\text{End-diastolic volume}}
  \]
1- Preload

- determines the ventricular end-diastolic pressure and volume
  = “atrial pressure”

\[ \uparrow \text{Preload} \rightarrow \uparrow \text{end-diastolic fiber length} \rightarrow \uparrow \text{force of contraction} \]

- In normal hearts

- In HF this response is reduced
  or even reversed

- In HF, preload increases because of:
  - \( \uparrow \) blood volume /and
  - \( \uparrow \) venous tone

- If preload > 20-25 mmHg \( \rightarrow \) Pulmonary congestion

- Treatments that reduces preload:
  - Salt restriction & diuretics \( \rightarrow \) reduce the high filling pressure
  - Vasodilators (e.g. nitroglycerine) \( \rightarrow \) redistributing the blood away from
    the chest into peripheral veins
2- Afterload

- The resistance against which the heart must pump blood;
  - Represented by: aortic impedance and SVR
    E.g: increased arterial pressure and obstruction to outflow
    (e.g. aortic stenosis)

- In HF, SVR will increase, because:
  - Circulating catecholamines
  - Activation of the RAAS (angiotensin II is a vasoconstrictor)

- Treatments that reduces afterload:
  - drugs that reduce arteriolar tone
Relationship between stroke volume and systemic vascular resistance. In an individual with normal left ventricular (LV) function, increasing systemic vascular resistance has little effect on stroke volume. **As the extent of LV dysfunction increases, the negative, inverse relationship between stroke volume and systemic vascular resistance becomes more important (B to A).**
3- Contractility of the heart

- The terms contractility is used to describe the cardiac muscle's inherent ability to develop force and shorten its fibers independent of preload or afterload.
- It is determined largely by the intrinsic strength and integrity of muscle cells.
- In HF: ↓ pump performance of the heart.
- Force of heart contraction is ↓ by:
  1. Ischemic heart disease
     MI, chronic severe ischemia
  2. Specific disorders affecting the heart muscle
     HTN and Myocarditis
  3. Disorders of heart muscle of unknown cause
     Idiopathic
- Heart increases contractility in response to +ve inotropic drugs.
4- Heart Rate

- Major determinant of CO.

- In HF:
  compensatory sympathetic activation of β-adrenoceptors comes into play to maintain CO

The workload and energy demands of a rapid heart rate ultimately place undo strain on the heart, however, and can eventually worsen HF.
5- Myocardial Compliance

- How easy the myocardial fibres can stretch
- An important determinant of ventricular filling and therefore of CO.

- Compliance can be decreased by:
  - Fibrosis
  - Hypertrophy
  - Ischemia
Compensatory Mechanisms in HF

• The manifestations of ↓ CO
  – The major direct consequence
    • ↓ exercise tolerance
    • Rapid muscular fatigue
  – The Other manifestations result from
    • The attempts by the body to compensate for the intrinsic cardiac defect in an attempt to maintain CO and oxygenation of vital organs.

• An understanding of the potential benefits and adverse consequences of the compensatory mechanisms is essential to understanding the signs, symptoms, and treatment of HF

• What are the compensatory mechanisms of the body?
Compensatory mechanisms

- These include:
  - increased sympathetic tone,
  - activation of the renin-angiotensin-aldosterone system (RAAS),
  - sodium and water retention,
  - other neurohormonal adaptations,
  - cardiac “remodeling” (ventricular dilation, cardiac hypertrophy, and changes in left ventricular lumen shape).

- The **long-term consequences** of these adaptive mechanisms can create more harm than good.
Compensatory Mechanisms: Myocardial Hypertrophy

• The most important intrinsic compensatory mechanism
  – The increase in muscle mass helps to maintain cardiac performance in the face of adverse effects such as pressure or volume overload, loss of functional tissue (e.g. MI) or decrease in the contractility.

• However, after initial beneficial effect, there will be:
  – Ischemic changes
  – Impairment of diastolic filling
  – Alteration of ventricular geometry
## Beneficial and detrimental effects of the compensatory responses in heart failure

<table>
<thead>
<tr>
<th>Compensatory Response</th>
<th>Beneficial Effects of Compensation</th>
<th>Detrimental Effects of Compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased preload (through Na(^+) and water retention)</td>
<td>Optimize stroke volume via Frank-Starling mechanism (whereby an increase in preload results in an increase in stroke volume)</td>
<td>Pulmonary and systemic congestion and edema formation</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>Maintain BP in face of reduced CO</td>
<td>Increased MVO(_2)</td>
</tr>
<tr>
<td></td>
<td>Shunt blood from nonessential organs to brain and heart</td>
<td>Increased afterload decreases stroke volume and further activates the compensatory responses</td>
</tr>
<tr>
<td>Tachycardia and increased contractility (because of SNS activation)</td>
<td>Helps maintain CO</td>
<td>Increased MVO(_2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shortened diastolic filling time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\beta_1)-receptor downregulation, decreased receptor sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precipitation of ventricular arrhythmias</td>
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<tr>
<td></td>
<td></td>
<td>Increased risk of myocardial cell death</td>
</tr>
<tr>
<td>Ventricular hypertrophy and remodeling</td>
<td>Helps maintain CO</td>
<td>Diastolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Reduces myocardial wall stress</td>
<td>Systolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Decreases MVO(_2)</td>
<td>Increased risk of myocardial cell death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased risk of myocardial ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased arrhythmia risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrosis</td>
</tr>
</tbody>
</table>
**Ventricular function (Frank-Starling) curve**

1. **NORMAL HEART**
   - Within limits, when cardiac muscle is stretched, its force of contraction increases and, hence, cardiac output increases.
   - However, if the ventricle is overly stretched, the effect of ventricular contraction is diminished.
   - A is the normal operating point in the healthy heart.

2. **DECOMPENSATED HEART FAILURE**
   - Initial reduction of contractility (A to B) due to HF.
   - Symptoms of low cardiac output develop—for example, dyspnea and edema.

3. **COMPENSATED HEART FAILURE**
   - Ventricular end-diastolic pressure increases (B to C) in an effort to maintain an adequate cardiac output.
   - The increased ventricular end-diastolic pressure causes symptoms of congestion—for example, dyspnea.

4. **DIGITALIS TREATMENT**
   - Administration of digitalis shifts the ventricular function curve toward normal.
   - Increased contractility (C to D) leads to increased cardiac output.
   - Decreased sympathetic reflexes and vascular tone cause a decrease in the ventricular end-diastolic pressure (D to E).
Common precipitants of decompensation

- Lack of compliance
- Uncontrolled hypertension
- Cardiac arrhythmias
- Inadequate therapy
- Administration of inappropriate medications or fluid overload
- Other
  - Acute anginal chest pain
  - Environmental factors
  - Pulmonary infection
  - Emotional stress
HF Models

- Older paradigms
  - cardiorenal model
    - problem viewed as excess Na\(^+\) & H\(_2\)O
    - diuretics main therapy
  - cardiocirculatory model
    - problem viewed as impaired CO
    - main therapies are positive inotropes, vasodilators

- Current paradigm: neurohormonal model
  - initiating event leads to decreased CO
  - becomes progressive systemic disease mediated by neurohormones & autocrine/paracrine factors
  - not a full explanation: drug therapies that target neurohormonal imbalances slow progression but do not stop disease progression
The neurohormonal model of heart failure and therapeutic insights it provides

Myocardial injury → Initial fall in LV performance → Activation of RAAS, SNS and other neurohormonal systems → Periphera vasoconstriction, hemodynamic alterations → Remodeling and progressive worsening of LV function → Heart failure symptoms → Morbidity and mortality

ACE inhibitors (ARBs), β-blockers, spironolactone → Diuretics, digoxin
Homework:

What is the role of natriuretic peptides in HF?

• Sources:
  1. ACCF/AHA 2009 Guidelines
  2. ESC 2008 Guidelines
Common clinical manifestations of HF

- The primary manifestations of heart failure are:
  - dyspnea and fatigue, which lead to exercise intolerance,
  - fluid overload, that can result in pulmonary congestion and peripheral edema.
- The presence of these signs and symptoms may vary considerably from patient to patient.
- Symptom severity often does not correlate with the degree of left ventricle dysfunction.
- It is also important to note that symptoms can vary considerably over time in a given patient.
- It is difficult to attribute a specific sign or symptom as caused by either right or left ventricular failure.

<table>
<thead>
<tr>
<th>Dominant clinical feature</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral oedema/congestion</td>
<td>Breathlessness, Tiredness, fatigue, Anorexia</td>
<td>Peripheral oedema, Raised jugular venous pressure, Pulmonary oedema, Hepatomegaly, ascites, Fluid overload (congestion), Cachexia</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>Severe breathlessness at rest</td>
<td>Crackles or rales over lungs, effusion, Tachycardia, tachypnoea</td>
</tr>
<tr>
<td>Cardiogenic shock (low output syndromes)</td>
<td>Confusion, Weakness, Cold periphery</td>
<td>Poor peripheral perfusion, SBP &lt;90 mmHg, Anuria or oliguria</td>
</tr>
<tr>
<td>High blood pressure (hypertensive heart failure)</td>
<td>Breathlessness, Breathlessness, Fatigue</td>
<td>Usually raised BP, LV hypertrophy, and preserved EF, Evidence of RV dysfunction, Raised JVP, peripheral oedema, hepatomegaly, gut congestion</td>
</tr>
<tr>
<td>Right heart failure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patient Presentation

- **Patient symptoms**
  - Shortness of breath, cough, orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion, edema, fatigue, weight gain

- **Physical signs**
  - Tachycardia, increasing weight, jugular venous distention or hepatojugular reflux, presence of $S_3$, laterally displaced apical impulse, pulmonary crackles or wheezes, hepatomegaly, peripheral edema
Non-specific Findings

- LVH on ECG
- Weakness, fatigue, exercise intolerance
- Confusion, lethargy, hallucinations, insomnia,
- Nightmares and headaches
- Pallor, cool extremities, cyanotic digits
- Renal dysfunction
Diagnosis of HF

• Clinical diagnosis is based on careful history and physical examination

• HF is characterized by
  – specific symptoms in medical history
    • (dyspnea and fatigue)
  – Specific signs on the physical examination
    • (edema, rales)

• **Remember**: Heart failure IS NOT equivalent to
  • cardiomyopathy
  • LV dysfunction;
  – these latter terms describe structural or functional reasons for the development of heart failure
## Clinical history in patients with HF

<table>
<thead>
<tr>
<th>History</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential clues suggesting etiology of HF</td>
<td>A careful family history may identify an underlying familial cardiomyopathy in patients with idiopathic DCM (118). Other etiologies outlined in Section 5 should be considered as well.</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>A patient with recent-onset systolic HF may recover over time (113).</td>
</tr>
<tr>
<td>Severity and triggers of dyspnea and fatigue, presence of chest pain,</td>
<td>To determine NYHA class; identify potential symptoms of coronary ischemia.</td>
</tr>
<tr>
<td>exercise capacity, physical activity, sexual activity</td>
<td></td>
</tr>
<tr>
<td>Anorexia and early satiety, weight loss</td>
<td>Gastrointestinal symptoms are common in patients with HF. Cardiac cachexia is associated with adverse prognosis (191).</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Rapid weight gain suggests volume overload.</td>
</tr>
<tr>
<td>Palpitations, (pre)syncope, ICD shocks</td>
<td>Palpitations may be indications of paroxysmal AF or ventricular tachycardia. ICD shocks are associated with adverse prognosis (192).</td>
</tr>
<tr>
<td>Symptoms suggesting transient ischemic attack or thromboembolism</td>
<td>Affects consideration of the need for anticoagulation.</td>
</tr>
<tr>
<td>Development of peripheral edema or ascites</td>
<td>Suggests volume overload.</td>
</tr>
<tr>
<td>Disordered breathing at night, sleep problems</td>
<td>Treatment for sleep apnea may improve cardiac function and decrease pulmonary hypertension (193).</td>
</tr>
<tr>
<td>Recent or frequent prior hospitalizations for HF</td>
<td>Associated with adverse prognosis (194).</td>
</tr>
<tr>
<td>History of discontinuation of medications for HF</td>
<td>Determine whether lack of GDMT in patients with HF_rEF reflects intolerance, an adverse event, or perceived contraindication to use. Withdrawal of these medications has been associated with adverse prognosis (195, 196).</td>
</tr>
<tr>
<td>Medications that may exacerbate HF</td>
<td>Removal of such medications may represent a therapeutic opportunity.</td>
</tr>
<tr>
<td>Diet</td>
<td>Awareness and restriction of sodium and fluid intake should be assessed.</td>
</tr>
<tr>
<td>Adherence to medical regimen</td>
<td>Access to medications; family support; access to follow-up; cultural sensitivity</td>
</tr>
<tr>
<td>Physical Examination</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------</td>
</tr>
<tr>
<td>BMI and evidence of weight loss</td>
<td>Obesity may be a contributing cause of HF; cachexia may correspond with poor prognosis.</td>
</tr>
<tr>
<td>Blood pressure (supine and upright)</td>
<td>Assess for hypertension or hypotension. Width of pulse pressure may reflect adequacy of cardiac output. Response of blood pressure to Valsalva maneuver may reflect LV filling pressures (197).</td>
</tr>
<tr>
<td>Pulse</td>
<td>Manual palpation will reveal strength and regularity of pulse rate.</td>
</tr>
<tr>
<td>Examination for orthostatic changes in blood pressure and heart rate</td>
<td>Consistent with volume depletion or excess vasodilation from medications.</td>
</tr>
<tr>
<td>Jugular venous pressure at rest and following abdominal compression (Heywood video)</td>
<td>Most useful finding on physical examination to identify congestion (187-190, 198).</td>
</tr>
<tr>
<td>Presence of extra heart sounds and murmurs</td>
<td>$S_3$ is associated with adverse prognosis in HFrEF (188). Murmurs may be suggestive of valvular heart disease.</td>
</tr>
<tr>
<td>Size and location of point of maximal impulse</td>
<td>Enlarged and displaced point of maximal impulse suggests ventricular enlargement.</td>
</tr>
<tr>
<td>Presence of right ventricular heave</td>
<td>Suggests significant right ventricular dysfunction and/or pulmonary hypertension.</td>
</tr>
<tr>
<td>Pulmonary status: respiratory rate, rales, pleural effusion</td>
<td>In advanced chronic HF, rales are often absent despite major pulmonary congestion.</td>
</tr>
<tr>
<td>Hepatomegaly and/or ascites</td>
<td>Usually markers of volume overload.</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>Many patients, particularly those who are young, may be not edematous despite intravascular volume overload. In obese patients and elderly patients, edema may reflect peripheral rather than cardiac causes.</td>
</tr>
<tr>
<td>Temperature of lower extremities</td>
<td>Cool lower extremities may reflect inadequate cardiac output.</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DCM, dilated cardiomyopathy; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricular; and NYHA, New York Heart Association.
Initial / Ongoing Evaluation

• Identify heart disease
• Assess functional capacity
  – NYHA, 6 min walk, …
• Assess volume status:
  – edema, rales, jugular, hepatomegaly, body weight
• Lab assessment:
  – routine: electrolytes, renal function
  – repeat ECHO, RX only if significant changes in functional status
• Assess prognosis
Making the Diagnosis

Diagnosis begins with the clinical examination

Primary symptoms  Dyspnea, fatigue, edema
Secondary symptoms  Paroxysmal nocturnal dyspnea, orthopnea, abdominal pain, nocturia, cough, anorexia
Primary physical signs  Elevated jugular venous pressure, S3 gallop, rales, edema
Secondary physical signs  Ascites, hepatomegaly, weight loss

Confirming the Diagnosis

Primary tests (for all patients)
- Left ventricular imaging (echocardiography, nuclear scan, angiography)
- Electrocardiogram
- Chest x-ray
- Complete blood count
- Urinalysis
- Blood urea nitrogen
- Serum creatinine
- Blood glucose
- Liver function tests
- Thyroid stimulating hormone
- Electrolytes, calcium, magnesium, and phosphorus

Secondary tests (use as clinically indicated)
- BNP (B-type natriuretic peptide)
- Testing to exclude ischemic heart disease
- Consider testing for hemochromatosis, thyrotoxicosis, lupus, leptospirosis, pheochromocytoma, AIDS, or Chagas disease

A look at the ventricle is essential
A. Chest x-ray with increased vascular markings (represents interstitial edema, early alveolar edema)
   Arrow: fluid in right lung fissure; cardiomegaly
B. Lateral chest x-ray view.
   Arrow: pulmonary effusion
Severe left ventricular dilation & increased left atrial dimension in end diastole (B); appears to be unchanged from end systole (A). The ventricular septum appears in a nearly identical position in both: represents akinesia.
Diagnosis of HF

Clinical examination, ECG, Chest X-ray, Echocardiography

Natriuretic peptides

- BNP <100 pg/mL  
  NT-proBNP < 400 pg/mL  
  Chronic HF unlikely

- BNP 100–400 pg/mL  
  NT-proBNP 400–2000 pg/mL  
  Uncertain diagnosis

- BNP >400 pg/mL  
  NT-proBNP > 2000 pg/mL  
  Chronic HF likely

*Figure 1* Flow chart for the diagnosis of HF with natriuretic peptides in untreated patients with symptoms suggestive of HF.
Table 8. Selected Causes of Elevated Natriuretic Peptide Concentrations

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Noncardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Heart failure, including RV syndromes</td>
<td>• Advancing age</td>
</tr>
<tr>
<td>• Acute coronary syndrome</td>
<td>• Anemia</td>
</tr>
<tr>
<td>• Heart muscle disease, including LVH</td>
<td>• Renal failure</td>
</tr>
<tr>
<td>• Valvular heart disease</td>
<td>• Pulmonary: obstructive sleep apnea, severe pneumonia, pulmonary hypertension</td>
</tr>
<tr>
<td>• Pericardial disease</td>
<td>• Critical illness</td>
</tr>
<tr>
<td>• Atrial fibrillation</td>
<td>• Bacterial sepsis</td>
</tr>
<tr>
<td>• Myocarditis</td>
<td>• Severe burns</td>
</tr>
<tr>
<td>• Cardiac surgery</td>
<td>• Toxic-metabolic insults, including cancer chemotherapy and envenomation</td>
</tr>
<tr>
<td>• Cardioversion</td>
<td></td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy; and RV, right ventricular.
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Diagnosis of heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supports if present</td>
</tr>
<tr>
<td>Compatible symptoms</td>
<td>+++</td>
</tr>
<tr>
<td>Compatible signs</td>
<td>++</td>
</tr>
<tr>
<td>Cardiac dysfunction on echocardiography</td>
<td>++++</td>
</tr>
<tr>
<td>Response of symptoms or signs to therapy</td>
<td>++++</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>+++</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
</tr>
<tr>
<td>Elevated BNP/NT-proBNP</td>
<td>++++</td>
</tr>
<tr>
<td>Low/normal</td>
<td>+</td>
</tr>
<tr>
<td>BNP/NT-proBNP</td>
<td></td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>+</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>+</td>
</tr>
<tr>
<td>Mild elevations of troponin</td>
<td>+</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary congestion</td>
<td>++++</td>
</tr>
<tr>
<td>Reduced exercise capacity</td>
<td>++++</td>
</tr>
<tr>
<td>Abnormal pulmonary function tests</td>
<td>+</td>
</tr>
<tr>
<td>Abnormal haemodynamics at rest</td>
<td>++++</td>
</tr>
</tbody>
</table>
Diagnostic Test Recommendations
(AHA/ACCF 2013)

Class I

1. Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone. *(Level of Evidence: C)*

2. Serial monitoring, when indicated, should include serum electrolytes and renal function. *(Level of Evidence: C)*

3. A 12-lead ECG should be performed initially on all patients presenting with HF. *(Level of Evidence: C)*

Class IIa

1. Screening for hemochromatosis or HIV is reasonable in selected patients who present with HF. *(Level of Evidence: C)*

2. Diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma are reasonable in patients presenting with HF in whom there is a clinical suspicion of these diseases. *(Level of Evidence: C)*
Biomarker Recommendations

A. Ambulatory/Outpatient

Class I

1. In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty (217-223). (Level of Evidence: A)

2. Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (222, 224-229). (Level of Evidence: A)

Class IIa

1. BNP- or NT-proBNP–guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolemic patients followed in a well-structured HF disease management program (230-237). (Level of Evidence: B)

Class IIb

1. The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established (230-237). (Level of Evidence: B)

2. Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF (238-244). (Level of Evidence: B)
B. Hospitalized/Acute

Class I

1. Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis (212, 245-250). *(Level of Evidence: A)*

2. Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF (248, 251-258). *(Level of Evidence: A)*

Class IIb

1. The usefulness of BNP- or NT-proBNP–guided therapy for acutely decompensated HF is not well-established (259, 260). *(Level of Evidence: C)*

2. Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF (248, 253, 256, 257, 261-267). *(Level of Evidence: A)*
Classification of HF
NYHA Functional Capacity

• **Class I:**
  – No limitation of physical activity. *Ordinary physical activity* does not cause undue fatigue, palpitation, dyspnea, or angina.

• **Class II:**
  – Slight limitation of physical activity. *Ordinary physical activity* results in fatigue, palpitation, dyspnea, or angina.

• **Class III:**
  – Marked limitation of physical activity. *Comfortable at rest, but less than ordinary physical activity* results in fatigue, palpitation, dyspnea, or angina.

• **Class IV:**
  – Unable to carry on any physical activity without discomfort. Symptoms present at rest. With any physical activity, symptoms increase.

**NYHA Classes - shift back/forth in individual patient (in response to Rx and/or progression of disease)**

ACC/AHA Stages of HF

STAGE A: High risk for developing HF
STAGE B: Asymptomatic LV dysfunction
STAGE C: Past or current symptoms of HF
STAGE D: End-stage HF

• Stages
  – Complement, DO NOT replace NYHA classes
  – progress in one direction due to cardiac remodeling

• This system is designed to:
  – emphasize preventability of HF through risk factor modification
  – recognize the progressive nature of LV dysfunction
Stages of HF

- **HF is a progressive disorder:**
  - Left ventricular dysfunction
    - begins with some injury to or stress on the myocardium
    - is generally a progressive process, even in the absence of a new identifiable insult to the heart.

- The principal manifestation of such progression
  - a change in the geometry of the left ventricle such as
    - cardiac remodeling.
      - the chamber dilates,
      - hypertrophies,
      - and becomes more spherical
# Stages of HF

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF (38)</th>
<th>NYHA Functional Classification (46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At high risk for HF but without structural heart disease or symptoms of HF</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but without signs or symptoms of HF</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
</tr>
</tbody>
</table>

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.
The Heart Failure Continuum

Stage A
- No structural heart disease (normal EF) but at high risk of HF
- Control risk factors for heart disease (HTN, hyperlipidemia, DM, tobacco use, etc.)
- Avoid cardiotoxins (alcohol, anthracyclines, cocaine, methamphetamine)
- Lifestyle modification

Stage B
- Structural heart disease (low EF), e.g. post-MI, HTN, valvular disease
- No current or past symptoms of HF (NYHA-FC I)
- Control risk factors for heart disease (HTN, hyperlipidemia, DM, tobacco use, etc.)
- Initiate ACEI or ARBs and beta-blockers in post-MI patients
- Lifestyle modification

Stage C
- Structural heart disease
- Current or past symptoms of HF (NYHA-FC I-IV)
- ACE inhibitors or ARBs and beta-blockers, diuretics for fluid retention
- Lifestyle modification (sodium and fluid restriction)
- Additional medications for select patients (digoxin, aldosterone antagonists, nitrates/hydralazine)
- Devices in select patients (biventricular pacemaker, implantable defibrillator)

Stage D
- Refractory HF (NYHA-FC IV) despite optimal therapy
- Evaluate for transplant, mechanical assistance, inotropic support, experimental interventions
- End of life care/hospice
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with MI, statins should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Blood pressure should be controlled to prevent symptomatic HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ACE inhibitors should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Beta blockers should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF</td>
<td>III: Harm</td>
<td>C</td>
</tr>
</tbody>
</table>
Treatment of Chronic Heart Failure

Goals of therapy
Pharmacologic management
Nonpharmacologic management
Goals of HF therapy

- Survival
- Morbidity
- Exercise capacity
- Quality of life
- Neurohormonal changes
- Progression of CHF
- Symptoms
General measures

- The complexity of the heart failure syndrome necessitates a comprehensive approach to management that includes:
  - accurate diagnosis,
  - identification and treatment of risk factors (e.g., diabetes, hypertension, coronary artery disease),
  - elimination or minimization of precipitating factors,
  - appropriate pharmacologic and nonpharmacologic therapy,
  - close monitoring and followup.

- Patient assessment:
  - History and patient examination
    - determine etiology
    - determine precipitating factors
  - Initial and ongoing assessment of activities of daily living (ADL) and volume status
  - Initial CBC, UA, electrolytes (Ca/Mg), BUN/Scr, BG, LFTs, TSH, EKG and Echo
  - Serial electrolytes and renal function
Nonpharmacological treatment of HF

- Maintenance of fluid balance
  - sodium restriction < 3 grams/day,
  - fluids to < 2 L/day (particularly in those not easily controlled with dietary sodium restriction and diuretics)
  - daily weights
- Tobacco and alcohol cessation
- Management of cardiac comorbidities (obesity, hypertension, hyperlipidemia, diabetes mellitus)
- Exercise:
  - Aerobic activity (stable NYHA I-III) – appears to improve functional status and slow HF progression
  - Restrict with acute congestive symptoms
- Patient and family counseling
- Immunizations
Nonpharmacological treatment of HF

- Coronary revascularization
- Biventricular pacing
- Enhanced external counterpulsation therapy
- Surgical ventricular restoration
- Left ventricular assist devices/Heart transplant
- Compassionate end of life care/hospice
Pharmacologic treatment of HF

• Standard drug therapies
  – Diuretic (if evidence of fluid retention)
  – ACE inhibitor or ARB (assuming no CI)
  – β-blocker

• Select patients
  – Digoxin (common)
  – Aldosterone antagonist
  – Nitrates/Hydralazine

• Other agents
  – Calcium Channel Blockers
  – Anticoagulation
  – Antiarrhythmics
HFrEF Stage C
NYHA Class I – IV

Treatment:

Class I, LOE A
ACEI or ARB AND
Beta Blocker

Change from previous recommendations

For all volume overload, NYHA class II-IV patients
Add
Class I, LOE C
Loop Diuretics

For persistently symptomatic African Americans, NYHA class III-IV
Add
Class I, LOE A
Hydral-Nitrates

For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL
Add
Class I, LOE A
Aldosterone Antagonist

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; HFrEF, heart failure with reduced ejection fraction; Hydral-Nitrates, hydralazine and isosorbide dinitrate; LOE, Level of Evidence; and NYHA, New York Heart Association.
### Table 18. Medical Therapy for Stage C HFrEF: Magnitude of Benefit Demonstrated in RCTs

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality (%)</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>7</td>
<td>33</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NNT, number needed to treat; RCTs, randomized controlled trials; and RR, relative risk.
Pharmacothrapeuic agents 
1- Diuretics

• Benefits:
  – Decrease Na and water retention → reduce preload
  – Decrease signs/symptoms of fluid retention
  – Improve exercise tolerance, quality of life
  – Improve cardiac function
  – Reduce HF hospitalizations

• Do not alter disease progression or prolong survival
• Should not be used alone in patients with HF
• All patients with evidence of fluid retention
• Many patients require chronic diuretic therapy to maintain euvolesia

• Body weight changes: sensitive marker of fluid retention/loss
  – daily weights to adjust diuretic therapy
  – Report weight gain of > 0.25-0.5 kg/day over several days
## Oral Diuretics Recommended for Use in the Treatment of Fluid Retention in Chronic Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Total Daily Dose</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5 to 1.0 mg once or twice</td>
<td>10 mg</td>
<td>4 to 6 hours</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20 to 40 mg once or twice</td>
<td>600 mg</td>
<td>6 to 8 hours</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 to 20 mg once</td>
<td>200 mg</td>
<td>12 to 16 hours</td>
</tr>
<tr>
<td><strong>Thiazide diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>250 to 500 mg once or twice</td>
<td>1000 mg</td>
<td>6 to 12 hours</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>12.5 to 25 mg once</td>
<td>100 mg</td>
<td>24 to 72 hours</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25 mg once or twice</td>
<td>200 mg</td>
<td>6 to 12 hours</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5 once</td>
<td>5 mg</td>
<td>36 hours</td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5 mg once</td>
<td>20 mg</td>
<td>12 to 24 hours</td>
</tr>
<tr>
<td><strong>Potassium-sparing diuretics†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>5 mg once</td>
<td>20 mg</td>
<td>24 hours</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25 mg once</td>
<td>50 mg*</td>
<td>2 to 3 days</td>
</tr>
<tr>
<td>Triamterene</td>
<td>50 to 75 mg twice</td>
<td>200 mg</td>
<td>7 to 9 hours</td>
</tr>
<tr>
<td><strong>Sequential nephron blockade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5 to 10 mg once plus loop diuretic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25 to 100 mg once or twice plus loop diuretic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide (IV)</td>
<td>500 to 1000 mg once plus loop diuretic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mg indicates milligrams; IV, intravenous. *Higher doses may occasionally be used with close monitoring. †Eplerenone, although also a diuretic, is primarily used in chronic heart failure as a suppressor of the renin-angiotensin-aldosterone system.
Table 5. Intravenous Diuretic Medications Useful for the Treatment of Severe Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Maximum Single Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1.0 mg</td>
<td>4 to 8 mg</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>160 to 200 mg</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 mg</td>
<td>100 to 200 mg</td>
</tr>
<tr>
<td><strong>Thiazide Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>500 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td><strong>Sequential Nephron Blockade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>500 to 1000 mg (IV) once or twice plus loop diuretics once; multiple doses per day</td>
<td></td>
</tr>
<tr>
<td>Metozaloxone (as Zaroxolyn or Diulo)</td>
<td>2.5 to 5 mg PO once or twice daily with loop diuretic</td>
<td></td>
</tr>
<tr>
<td><strong>IV Infusions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1-mg IV load then 0.5 to 2 mg per hour infusion</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>40-mg IV load then 10 to 40 mg per hour infusion</td>
<td></td>
</tr>
<tr>
<td>Torsemide</td>
<td>20-mg IV load then 5 to 20 mg per hour infusion</td>
<td></td>
</tr>
</tbody>
</table>
Thiazide Diuretics

• Weak diuretics
  – more persistent antihypertensive activity than loop diuretics
  – infrequently used alone in HF

• Can use with loop diuretics to promote diuresis

• Preferred in some patients with mild fluid retention & elevated BP
Loop Diuretics

- Furosemide, bumetanide, toresmide
- **Mainstay of HF therapy**
- Efficacy reduced by:
  - competitors of the organic acid transport pathway,
  - excess dietary Na\(^+\),
  - co-administration with NSAIDs
- **Efficacy maintained in impaired renal function**
- Once **ceiling dose** reached, additional diuresis achieved through increased frequency rather than increased dose.
  - Ceiling dose: single dose above which additional response is unlikely to be observed
- Cause metabolic abnormalities such as hypokalemia, hypomagnesemia
Diuretics

Initiation and Maintenance

• Loop diuretics are the mainstay of therapy
• **Low doses with titration** until urine output increases, and weight decreases (generally by 0.5 to 1 kg daily)
• **Sodium restriction** vital
• May need to tolerate some degree of hypotension and/or renal insufficiency until fluid retention resolved.
• If patient develops **hypotension or renal decline** while on diuretics assess whether it is d/t the diuretic or disease:
  – Fluid retention is disease (↑ dose of diuretic)
  – No fluid retention is diuretic (↓ dose of diuretic)
• Once fluid retention resolved **maintenance dose** should be continued with dose reassessed and adjusted periodically
• Patients should be educated on **self-adjustment** based on weight and symptoms
• May need to **use 2 or more diuretics** (thiazide + loop) in combination for enhanced effect
• **End stage HF patients** may require ↑ dose b/c:
  – bowel edema or hypoperfusion may ↓ absorption /OR
  – decreased renal blood flow may reduce delivery.
## 2- ACE Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Captopril</td>
<td>H, DN</td>
<td>Post MI</td>
<td>HF</td>
</tr>
<tr>
<td>Enalapril</td>
<td>H, DN</td>
<td>Asymptomatic LVSD</td>
<td>HF</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>H</td>
<td>-</td>
<td>HF</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>H, DN</td>
<td>Post MI</td>
<td>HF</td>
</tr>
<tr>
<td>Moexipril</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perindopril</td>
<td>H, CV Risk</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quinapril</td>
<td>H</td>
<td>-</td>
<td>HF</td>
</tr>
<tr>
<td>Ramipril</td>
<td>H, CV Risk</td>
<td>Post MI</td>
<td>Post MI</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>H</td>
<td>Post MI</td>
<td>Post MI</td>
</tr>
</tbody>
</table>

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Asymptomatic LVSD, Asymptomatic left ventricular systolic dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.
Inhibitors of the Renin-Angiotensin-Aldosterone System and Beta-Blockers Commonly Used for the Treatment of Patients With Heart Failure With Low Ejection Fraction (Slide 1 of 2)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Dose(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3 times</td>
<td>50 mg 3 times</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice</td>
<td>10 to 20 mg twice</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5 to 10 mg once</td>
<td>40 mg once</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5 mg once</td>
<td>20 to 40 mg once</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg once</td>
<td>8 to 16 mg twice</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg twice</td>
<td>20 mg twice</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 to 2.5 mg once</td>
<td>10 mg once</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg once</td>
<td>4 mg once</td>
</tr>
<tr>
<td><strong>Angiotensin Receptor Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 to 8 mg once</td>
<td>32 mg once</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 to 50 mg once</td>
<td>50 to 100 mg once</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20 to 40 mg twice</td>
<td>160 mg twice</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin converting enzyme; mg, milligrams; and kg, kilograms.
Inhibitors of the Renin-Angiotensin-Aldosterone System and Beta-Blockers Commonly Used for the Treatment of Patients With Heart Failure With Low Ejection Fraction (Slide 2 of 2)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Dose(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aldosterone Antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25 mg once</td>
<td>25 mg once or twice</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once</td>
<td>50 mg once</td>
</tr>
<tr>
<td><strong>Beta-Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once</td>
<td>10 mg once</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice</td>
<td>25 mg twice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg twice for patients over 85 kg</td>
</tr>
<tr>
<td>Metoprolol succinate extended</td>
<td>12.5 to 25 mg once</td>
<td>200 mg once</td>
</tr>
<tr>
<td>release (metoprolol CR/XL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACE indicates angiotensin converting enzyme; mg, milligrams; and kg, kilograms.
ACE Inhibitors

• Cornerstone of HF pharmacotherapy
  – captopril, enalapril, lisinopril, quinapril, ramipril, fosinopril, trandolapril, perindopril
  – not all FDA approved for HF

• Actions:
  – Decrease preload
  – Decrease afterload
  – Decrease sympathetic activation
  – Decrease left ventricular hypertrophy, dilation and remodeling associated with HF → slow progression of HF
ACE Inhibitors

• Benefits:
  – Effective for preventing HF development, reducing CV risk
  – Alleviate symptoms and improve clinical status (prevent RAAS mediated worsening of myocardial function)
  – Enhance overall sense of well being (QOL)
  – ↓ Mortality (improve survival 20 to 30% compared to placebo)
  – ↓ Hospitalizations

• Place in therapy
  – All patients with left systolic HF should be taking ACE-I for morbidity/mortality benefits

  – For patients with C/I or those unable to tolerate ACE-I, alternative therapy with ARBs or hydralazine/nitrate combination is recommended
    • ARBs are appropriate alternatives in those patients in which a cough is troublesome, as this is a bradykinin mediated effect. Role of ARBs in patients with angioedema controversial
    • Hydralazine/Isosorbide dinitrate should be used if the patients renal dysfunction, hyperkalemia or hypotension is uncontrollable. This combo can also be used in those patients who develop angioedema to ACEIs
ACE Inhibitors

- Often underdosed & underutilized due to concerns about safety/adverse reactions, especially in patients with underlying renal dysfunction or hypotension

- Low doses okay, small difference in mortality outcomes between high & low doses

- ACE inhibitors should be initiated before β-blockers but the greatest benefit is with co-administration

- Risk factors for hypotension: hyponatremia, hypovoleemia, overdiuresis
ACE Inhibitors

Initiation and Maintenance

• Low doses with K+ and renal function checked within 1 to 2 weeks and periodically after.

• Titrated as tolerated to doses demonstrated to provide a clinical benefit or to moderate-high to high doses
  – Studies evaluating ACE-I titrated to a target dose NOT therapeutic response
  – Studies evaluating other drugs on top of ACE-I usually had at least intermediate doses of ACE-I given

• Concurrent diuretic therapy may need to be adjusted initially or after therapy started

• 85 to 90% of patients can tolerate short- and long-term therapy

IMP.

• Do not abruptly withdraw ACE-I’s b/c the patient can acutely deteriorate.

• Decrease dose gradually, unless patient is experiencing a life threatening reaction.
ACE Inhibitors

- **Contraindications:**
  - Bilateral renal artery stenosis
  - Unilateral stenosis of single functioning kidney
  - History of angioedema
  - Pregnancy category C in 1st trimester
  - Pregnancy category D in 2nd & 3rd trimester
  - K+ > 5.5 mmol/L that cannot be reduced

- **Precautions:**
  - Renal impairment (creatinine ≥ 3mg/dL)
  - Systolic BP < 80 mmHg
ACE Inhibitors

- **Adverse effects:**
  - Cough (5-10% of Caucasian patients, 50% of Chinese)
  - Hypotension
  - Renal insufficiency
  - Hyperkalemia
  - Angioedema (<1%, more frequent in blacks)
  - Renal insufficiency (5-30% incidence of increase in serum creatinine of > 0.3 mg/dl)
  - Rash
  - Taste disturbance

- **Homework:**
  - Mechanism of acute renal failure induced by ACEIs
  - Source: Applied Therapeutics, ch. 18
ACE Inhibitors

Management of ACEI Side-Effects

• Hypotension and dizziness
  – Concerned only if the patient presents with symptoms (worsening renal function, blurred vision, syncope)
  – Seen in 1st few days of initiation or titration
  – Highest risk in hypovolemic and hyponatremic (Na<130) patients
  – Try to decrease the diuretic dose and/or increase sodium intake, as long as there is not significant fluid retention

• Worsening Renal Function
  – Highest risk in hyponatremia, Class IV Heart Failure and those patients with BRAS or taking NSAIDs
  – Usually responds to decreased diuretic dose, while continuing ACEI
  – If fluid retention exists and the diuretic dose can not be decreased, may need to tolerate mild-moderate renal dysfunction to maintain therapy, b/c of significant benefits of ACEIs
ACE Inhibitors

• Cough
  – Occurs in 5-10% of Caucasian patients, 50% of Chinese
  – Non-productive, persistent tickle in the back of throat that occurs within 1st month of therapy
  – If D/C will disappear within 1-2 wks and reoccur upon rechallenge with ACEI
  – Exclude pulmonary causes of cough

• Hyperkalemia
  – Highest risk in patients receiving potassium supplementation or if renal function is impaired

• Angioedema
  – Occurs in <1% of patients, but is life threatening, therefore clinical suspicion warrants avoidance of ACEIs
  – Do not initiate ACEI in any patient with history of angioedema
## 3- β-Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Atenolol</td>
<td>H</td>
<td>Post MI</td>
<td>-</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>H</td>
<td>-</td>
<td>HF</td>
</tr>
<tr>
<td>Carteolol</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>H</td>
<td>Post MI</td>
<td>HF, Post MI</td>
</tr>
<tr>
<td>Labetalol</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>H</td>
<td>-</td>
<td>HF</td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>H</td>
<td>Post MI</td>
<td>-</td>
</tr>
<tr>
<td>Nadolol</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pindolol</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Propranolol</td>
<td>H</td>
<td>Post MI</td>
<td>-</td>
</tr>
<tr>
<td>Timolol</td>
<td>H</td>
<td>Post MI</td>
<td>-</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>-</td>
<td>-</td>
<td>HF</td>
</tr>
</tbody>
</table>

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Asymptomatic LVSD, Asymptomatic left ventricular systolic dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.
β-Blockers

• Multiple randomized controlled trials show specific β-blockers reduce morbidity & mortality in HF patients
  – carvedilol, metoprolol succinate, bisoprolol
  – not a class effect, not all β-blockers show benefit
  – several studies stopped early due to overwhelming benefit

• Mechanism of Action
  – Cardiac myocyte protection of receptors from catecholamines
  – Prevention of binding of auto-antibodies to adrenoceptors
  – Heart rate reduction
    • Improved (diastolic) coronary artery flow and → myocardial oxygenation
    • Improved force-frequency relationship
    • Cardiac myocyte energy conservation
β-Blockers

• Benefits:
  – Improve Symptoms
  – Improve clinical status
  – Enhance overall sense of well being (QOL)
  – decrease HF progression
  – ↓ Hospitalizations
  – ↓ Mortality (improve survival)
β-Blockers

• β-blockers should be **used in all stable HF patients with reduced LVEF in the absence of CIs or history of intolerance**
  • give even if asymptomatic or well controlled on diuretics & ACE-I’s

• **Initiate β-blockers after ACE inhibitors**
  – can use 1st in patients with excess SNS activity (tachycardia) or impaired renal function that precludes starting with an ACE inhibitor

• Package insert suggest at least 1 month stability before initiation
• Recent data and current guidelines suggest that drug can be safely initiated in hospital

• **Risk of decompensation** due to negative inotropic effects
  – start in stable patients with no or minimal fluid overload
  – dose dependent response for mortality prevention
β-Blockers

Initiation and Maintenance

- Very low doses with titration (every 2 weeks in trials) after demonstrated tolerability of dose
- Titrated as tolerated (over 6-8 wks) to doses demonstrated to provide a clinical benefit
- Studies evaluating beta-blockers titrated to a target or maximally tolerated dose NOT therapeutic response

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg bid</td>
<td>25 mg bid(^a)</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg daily</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5 – 25 mg daily</td>
<td>200 mg daily</td>
</tr>
</tbody>
</table>

\(^a\) Target dose for patient > 85 kg is 50 mg bid.
β-Blockers

• Concurrent diuretic therapy may need to be adjusted initially or after therapy started
• 85% of patients can tolerate short- and long-term therapy
• Patients should be monitored closely for worsening HF symptoms or S/Es
• Clinical responses may not become apparent for 2-3 months

• Should not be abruptly withdrawn b/c the patient can acutely deteriorate.
  → Decrease dose gradually, unless patient is experiencing a life threatening reaction.

• If on a B-blocker for >3months and heart failure worsens, it’s probably not d/t the B-blocker, but rather progression of disease or an exacerbation for some other reason
  – Increase dose of diuretic, do not D/C B-blocker for above reason, unless hypoperfusion is an issue
Recent update:

• whether beta-blocker dose or degree of heart rate reduction is the optimal endpoint to guide dose-titration and predict survival remains uncertain.

• In a recent meta-analysis, heart rate reduction and beta-blocker dose were compared as predictors of survival in patients with heart failure

• The results from this study suggest that the degree of beta-blocker mediated reduction in resting heart rate, but not beta-blocker dose, is associated with the magnitude of improved survival.

• Some published reports are consistent with these findings, whereas others have found no relationship between heart rate reduction and clinical outcomes with beta-blockers. All of these analyses are limited by their retrospective design, inability to account for other factors affecting heart rate (e.g., vagal activity, beta-receptor pharmacogenomics) and reliance on resting heart rate as a surrogate marker for extent of beta-blockade.

• Although resting heart rate is routinely used clinically to evaluate extent of beta-blockade, it is not as accurate as inhibition of exercise heart rate. Whether magnitude of resting heart rate reduction or achievement of clinical trial doses is the optimal surrogate marker for improved outcomes with beta-blockers in heart failure remains uncertain and may only be definitively determined by prospective trials.

**β-Blockers**

- Counseling of HF patients started on B-blockers:
  - Possibility of worsening of symptoms initially
    - Monitor for increased SOB, wt gain…
  - Need for slow upward dose titration
  - Long term benefit of therapy that make initial difficulties (if they occur) worth sticking through
β-Blockers

• **Absolute contraindications:**
  – uncontrolled bronchospastic disease
  – symptomatic bradycardia
  – advanced heart block (2\textsuperscript{nd} or 3\textsuperscript{rd} degree) without a pacemaker

• **Precautions:**
  – Asthma
  – Severe peripheral arterial disease
  – Uncompensated HF
β-Blockers

- Adverse effects:
  - Cold peripheries
  - Bronchoconstriction
  - Interference with autonomic and metabolic response to hypoglycemia
  - Bradycardia
  - Heart block
  - Hypotension
  - Fatigue
  - Worsening HF
β-Blockers

Management of Adverse Events

• Fluid retention and worsening heart failure- more likely to occur during initiation and first several months
  – Daily weights and careful adjustment of diuretics

• Hypotension- more likely with carvedilol (administer with food)
  – Administer ACE-I separately or temporarily reduce ACEI

• Bradycardia and heart block- risk of 5-10% as dose increased
  – If symptomatic or > 1st degree block need to reduce dose

• Fatigue/Weakness- may resolve with time or reduction in dose
4- Digoxin

- **Mechanism of action**
  - Inhibit Na+/K+/ATPase pump in cardiac cells → increased contractility
  - Inhibit Na+/K+/ATPase pump in non-cardiac cells → sensitization of cardiac baroreceptors decreasing sympathetic CNS outflow
  - Inhibit Na+/K+/ATPase pump in renal cells → reduction in renal tubular absorption of sodium and increased presentation to distal tubules → suppression of renin secretion
Digoxin

• Exact mechanism of benefit in HF is unclear but probably not +ve inotropic effect.

• Benefits likely to be from neurohormononal inhibition
  – Decrease sympathetic outflow
  – Improved baroreceptor function and increase vagal tone

• Benefits seen with low plasma concentrations; little added benefit at higher doses
  – target 0.5 to 1.0 ng/mL
Digoxin

• **Efficacy in heart failure**
  – Short term studies
  – Withdrawal studies
  – One long-term prospective, randomized, study (DIG Trial)

• **Digitalis Investigational Group (DIG trial)**
  – no significant difference in mortality
  – decreased morbidity

• Other studies show improved
  – LVEF
  – quality of life
  – exercise tolerance
  – HF symptoms

• **There is no survival benefit**
Digoxin

- **Place in therapy:**
  - Clinical studies show no evidence of slowing disease progression or decreased mortality
  - Its primary use is in patients who remain symptomatic on ACE-I’s (or alternative therapies), diuretics and B-blockers.
  - First line therapy in HF with supraventricular tachycardia (e.g. atrial fibrillation) for its ventricular rate control properties
  - Beneficial in symptomatic/stage C HF & reduced LVEF → *reduce hospitalization*
Digoxin

Initiation and Maintenance

• Do not need to “load” patient
• 0.125mg PO QD or QOD
  – If >70 yo, impaired renal function, low body mass
• 0.25mg PO QD
  – Rarely needed for HF

• Baseline level reasonable and again if changes in clinical condition, suspicion of toxicity, changes in renal function
  – 0.8-1.0 is optimal
  – >1.0
    • increases toxicity with no extra added benefit for heart failure
Digoxin

• **Contraindications**
  – 2-3<sup>rd</sup> degree heart block (without PM)
  – Wolff-Parkinson-White with Afib
  – Ventricular fibrillation
  – Hypersensitivity

• **Precautions**
  – Amyloid cardiomyopathy
  – Idiopathic hypertrophic subaortic stenosis
  – Constrictive pericarditis
  – Others...
Digoxin

- **Adverse Reactions**
  - Heart block
  - CNS (dizziness, visual disturbances, confusion, weakness)
  - Dermatologic: rash (1.6%)
  - Gastrointestinal: nausea, vomiting, diarrhea
  - Others: Increased estrogen levels, impotence
**Digoxin**

Adverse effects more common in selected patients

- renal dysfunction
- lean body mass
- elderly
- interacting drugs
- hypokalemia
- hypomagnesia
- hypercalcemia
- hypothyroidism
- MI
- acidosis

Treat based on symptoms, not plasma concentration (usually > 2 ng/ml)
Treat cardiac arrhythmias, electrolyte abnormalities

**Homework:**
Drug interactions with digoxin
Source: Koda-Kimble, table 18-15
5- Aldosterone Antagonists

Pathophysiologic Mechanisms of Aldosterone in Heart Failure

Angiotensin II, K⁺, ACTH

Adrenal

Myocardial/Vascular

↑ Aldosterone

↑ Fibroblast Collagen Synthesis

VSMC Hypertrophy

↑ Free Radical Production

↓ NO (in adrenal)

↑ AT1R Binding of Ang II

↑ ACE Activity

↑ PAI-1

↑ ET-1

VSMC=vascular smooth muscle cell; NO=nitric oxide; ET-1=endothelin-1.
Aldosterone Antagonists

• Spironolactone, eplerenone

• **Mechanism of action**
  – Block aldosterone binding at mineralcorticoid receptors in kidney, heart, blood vessels, and brain
  – Blockade of aldosterone in distal renal tubule $\rightarrow$ increase NaCl and water excretion and potassium retention

• **Efficacy in heart failure**
  – Spironolactone reduced total mortality 30% over 2 years in NYHA late III and IV patients
Aldosterone Antagonists

Place in therapy

- Recommended in Class IV and Class III with recent hospitalization, despite therapy with ACEI, Diuretics, +/- Digoxin, +/- B-blocker
  - Careful selection and monitoring based on renal function and K levels

- Reasonable in any patient requiring K supplementation
  - May be able to reduce/eliminate K dose

- May consider in post MI patients with reduced LV function
Aldosterone Antagonists

• **Adverse Reactions**
  – Serious hyperkalemia ($\geq 6.0$ mmol/L): 5%
  – Renal insufficiency
  – Gynecomastia/breast pain (10% spironolactone)
  – Rash

• **Listed contraindications (eplerenone)**
  – Serum potassium $>5.5$ mEq/L at initiation
  – Creatinine clearance $<30$ mL/min
  – Concomitant use with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir
Aldosterone Antagonists

Reducing Hyperkalemia Risk

• Avoid aldosterone antagonists in patients with the following:
  – SCr > 2.0 in women or > 2.5 mg/dL in men
  – CrCl < 30 mL/min
  – recent worsening of renal function
  – serum K+ ≥ 5.0 mEq/L
  – history of severe hyperkalemia

• Start with low doses (12.5 mg/day spironolactone, 25 mg/day eplerenone)
  – especially
    • elderly
    • DM
    • CrCl < 50 mL/min

• Decrease/discontinue K+ supplements when starting an aldosterone antagonist

• If K rises to >5.4, decrease spironolactone dose

• Avoid ACE inhibitor, ARB, aldosterone antagonist triple therapy
# 6- Angiotensin II Receptor Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin Receptor Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>H</td>
<td>-</td>
<td>HF</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>H, DN</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Losartan</td>
<td>H, DN</td>
<td>CV Risk</td>
<td>-</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Valsartan</td>
<td>H, DN</td>
<td>Post MI</td>
<td>Post MI, HF</td>
</tr>
<tr>
<td><strong>Aldosterone Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>H</td>
<td>Post MI</td>
<td>Post MI</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>H</td>
<td>-</td>
<td>HF</td>
</tr>
</tbody>
</table>

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Asymptomatic LVSD, Asymptomatic left ventricular systolic dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.
ARBs

- Use controversial in HF
  - valsartan, candesartan shown beneficial in trials

- ARBs have **theoretical advantage** over ACE inhibitors:
  - ACE inhibitors have ACE escape which leads to increased angiotensin II & aldosterone
  - no effect on bradykinin (lower incidence of cough)
  - not metabolized by cytochrome P-450; no significant drug-drug interactions
ARBs

- **Are they interchangeable with ACE-I’s?**
  - Some evidence of similar benefits to ACE-I’s
  - No evidence of superiority to ACE-I’s
  - Should not be used as 1st line therapy for HF (in place of ACE-I’s
  - Should not be considered interchangeable with ACE-I’s

- **In patients with ACE-I CI or intolerance, are ARB’s appropriate alternative therapy?**
  - Reasons for CI or intolerance include elevated K, renal impairment, angioedema, rash, cough
  - ARB’s similarly problematic as ACE-I’s for elevated K, and renal impairment
  - Good alternative for patients who experience angioedema or cough on ACE-I’s
**ARBs**

**Place in therapy**

- Current guidelines recommend ARBs as an alternative to ACE inhibitors due to intolerance (cough, angioedema)
  - caution in angioedema, cross reactivity reported
  - not an alternative to ACE inhibitors for hypotension or renal insufficiency

- Current guidelines recommend addition of ARBs in some patients who remain symptomatic or hypertensive despite conventional heart failure therapy

- ACE-I, ARB and aldosterone antagonist concomitant use is strongly discouraged due to hyperkalemia risk
ARBS

- **Adverse effects:**
  - hypotension
  - decreased renal function
  - increased serum K⁺

- **Contraindications:**
  - pregnancy category C in 1\textsuperscript{st} trimester
  - pregnancy category D in 2\textsuperscript{nd} & 3\textsuperscript{rd} trimester
7- Nitrates & Hydralazine

- **Nitrates**: nitric oxide donors lead to venodilation & decreased preload
  - 40 mg q 6-8 hrs
  - Tolerance is not evident in HF

- **Hydralazine**: direct vasodilator leads to decreased SVR, increased SV, CO
  - 75 mg q 6-8 hrs
  - antioxidant properties, prevents nitrate tolerance
  - Side effects are common

- Combination provide balanced vasodilation
- Combination may be beneficial due to improving NO availability and reduced oxidative stress

- particularly effective in African Americans
  - 43% decrease in all cause mortality
  - possibly due to decreased nitric oxide; may benefit from therapy that enhances nitric oxide bioavailability
Nitrates & Hydralazine

NITRATES
HEMODYNAMIC EFFECTS

1- VENOUS VASODILATATION

↓ Preload

- Pulmonary congestion
- Ventricular size
- Vent. Wall stress
- MVO₂

2- Coronary vasodilatation

↑ Myocardial perfusion

3- Arterial vasodilatation

↓ Afterload

- Cardiac output
- Blood pressure

4- Others
Nitrates & Hydralazine

• Current guidelines:
  – add to standard therapy in African Americans with moderate-severe to severe HF or other ethnicities who have symptoms despite standard therapy
  – 1st line if unable to tolerate ACE inhibitors/ARBs due to renal insufficiency, hyperkalemia, hypotension

• Require frequent dosing

• Combination marketed as BiDil®

• **Adverse effects:**
  – headache
  – dizziness
  – GI distress
8. Calcium Channel Blockers

• No role in treating chronic heart failure associated with LV systolic dysfunction

• Newer agents (felodipine ER, amlodipine) may be used safely for other indications (i.e. angina, hypertension) in patients with chronic heart failure

Anticoagulants

• Most justified in patients with heart failure who have had a previous embolic event or are in atrial fibrillation
7.3.2.8.1. Anticoagulation: Recommendations

Class I

1. Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy* (508-514). (Level of Evidence: A)

2. The selection of an anticoagulant agent (warfarin, dabigatran, apixaban, or rivaroxaban) for permanent/persistent/paroxysmal AF should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in the international normalized ratio therapeutic range if the patient has been taking warfarin. (Level of Evidence: C)

Class IIa

1. Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke* (509-511, 515-517). (Level of Evidence: B)

Class III: No Benefit

1. Anticoagulation is not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source (518-520). (Level of Evidence: B)

*In the absence of contraindications to anticoagulation.
9. Antiarrhythmic therapy

- Patients with heart failure may have frequent and complex ventricular arrhythmias and a high risk of sudden death.

- Class I or III antiarrhythmic drugs are not recommended in patients with HF for the prevention of ventricular arrhythmias.

- The use of antiarrhythmic medication is not indicated as primary treatment for asymptomatic ventricular arrhythmias or to improve survival in patients with HF.

- It is reasonable to prescribe amiodarone to decrease recurrence of atrial arrhythmias and to decrease recurrence of ICD discharge for ventricular arrhythmias.

- ICD’s clearly superior to antiarrhythmic drugs in the prevention of sudden cardiac death (SCD).
Stage D HF Treatment

• Stage D patients
  – symptoms at rest refractory to maximal medical care
  – undergo recurrent hospitalizations
  – cannot be discharged from the hospital without special intervention

• Specialized therapies
  – mechanical circulatory support
  – continuous IV positive inotrope
  – cardiac transplant
  – hospice care
## Putting it All Together: Clinical Applications

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics are recommended in patients with HFrEF with fluid retention</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors are recommended for all patients with HFrEF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARBs are recommended in patients with HFrEF who are ACE inhibitor intolerant</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ARBs are reasonable as alternatives to ACE inhibitors as first-line therapy in HFrEF</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>Addition of an ARB may be considered in persistently symptomatic patients with HFrEF on GDMT</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Routine <em>combined</em> use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful</td>
<td>III: Harm</td>
<td>C</td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>Aldosterone receptor antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV who have LVEF ≤35%</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
### Putting it all together; continue

| Aldosterone receptor antagonists are recommended following an acute MI who have LVEF $\leq 40\%$ with symptoms of HF or DM | I | B |
| Inappropriate use of aldosterone receptor antagonists may be harmful | III: Harm | B |

**Hydralazine and isosorbide dinitrate**

| The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III–IV HF$\text{r}$EF on GDMT | I | A |
| A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF$\text{r}$EF who cannot be given ACE inhibitors or ARBs | IIa | B |

**Digoxin**

| Digoxin can be beneficial in patients with HF$\text{r}$EF | IIa | B |

**Anticoagulation**

<p>| Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy* | I | A |
| The selection of an anticoagulant agent should be individualized | I | C |
| Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke* | IIa | B |
| Anticoagulation is not recommended in patients with chronic HF$\text{r}$EF without AF, a prior thromboembolic event, or a cardioembolic source | III: No Benefit | B |</p>
<table>
<thead>
<tr>
<th><strong>Statins</strong></th>
</tr>
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<tbody>
<tr>
<td>Statins are not beneficial as adjunctive therapy when prescribed solely for HF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Omega-3 fatty acids</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HFrEF or HFpEF patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Other drugs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional supplements as treatment for HF are not recommended in HFrEF</td>
</tr>
<tr>
<td>Hormonal therapies other than to correct deficiencies are not recommended in HFrEF</td>
</tr>
<tr>
<td>Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn</td>
</tr>
<tr>
<td>Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Calcium channel blockers</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blocking drugs are not recommended as routine treatment in HFrEF</td>
</tr>
</tbody>
</table>
Statin therapy has been broadly implicated in prevention of adverse cardiovascular events, including new-onset HF. Originally designed to lower cholesterol in patients with cardiovascular disease, statins are increasingly recognized for their favorable effects on inflammation, oxidative stress, and vascular performance. Several observational and post analyses from large clinical trials have implied that statin therapy may provide clinical benefit to patients with HF. However, 2 large RCTs have demonstrated that rosvuastatin has neutral effects on long-term outcomes in patients with chronic HFrEF when added to standard GDMT.

At present, statin therapy should not be prescribed primarily for the treatment of HF to improve clinical outcomes.
Supplementation with omega-3 PUFA has been evaluated as an adjunctive therapy for cardiovascular disease and HF. Trials in primary and secondary prevention of coronary heart disease showed that omega-3 PUFA supplementation results in a 10% to 20% risk reduction in fatal and nonfatal cardiovascular events.

The GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico ) Prevenzione trial demonstrated a 21% reduction in death among post-MI patients taking 1 g of omega-3 PUFA (850 to 882 mg of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] as ethyl esters in the ratio of 1:1.2). The use of omega-3 PUFA supplementation is reasonable as adjunctive therapy in patients with chronic HF.
Class III: No Benefit

1. Nutritional supplements as treatment for HF are not recommended in patients with current or prior symptoms of HFrEF (544, 545). *(Level of Evidence: B)*

2. Hormonal therapies other than to correct deficiencies are not recommended for patients with current or prior symptoms of HFrEF. *(Level of Evidence: C)*

Class III: Harm

1. Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HFrEF are potentially harmful and should be avoided or withdrawn whenever possible (e.g., most antiarrhythmic drugs, most calcium channel blocking drugs (except amlodipine), NSAIDs, or thiazolidinediones) (546-557). *(Level of Evidence: B)*

2. Long-term use of infused positive inotropic drugs is potentially harmful for patients with HFrEF, except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment (see recommendations for stage D). *(Level of Evidence: C)*
Concomitant Disorder Treatment

• Hypertension
  – 2/3 HF patients have history of or current hypertension
  – 1\textsuperscript{st} line: ACE inhibitors, β-blockers, diuretics
  – 2\textsuperscript{nd} line: ARBs, aldosterone antagonists, isosorbide dinitrate/hydralazine or 2\textsuperscript{nd} generation CCBs (amlodipine, felodipine)
  – Avoid CCBs with negative inotropic effects & direct acting vasodilators that cause Na\textsuperscript{+} retention in patients with systolic dysfunction
Concomitant Disorder Treatment

- **Angina**
  - coronary artery disease: most common HF etiology
  - 1st line: nitrates, β-blockers
  - must be fluid controlled for antianginal medications to be effective
Concomitant Disorder Treatment

- **Atrial fibrillation**
  - 10 to 30% HF patients
  - 1\textsuperscript{st} line: ACE inhibitors, ARBs, β-blockers
  - digoxin slows ventricular response but not HF progression; β-blocker + digoxin better than either alone
  - avoid CCBs with negative inotropic function
  - amiodarone: preferred antiarrhythmic, dofetilide also safe & effective; avoid class I antiarrhythmic agents
  - increases risk of thromboembolism, decreases CO, leads to hemodynamic compromise
Concomitant Disorder Treatment

• Antithrombotic therapy for atrial fibrillation
  – high risk patients: paroxysmal, persistent, or permanent atrial fibrillation (target INR range 2 to 3) at high risk for stroke
    • warfarin
  – intermediate risk patients (age 65 to 75, no stroke risk factors)
    • warfarin or ASA 325 mg/day depending on risk factors
  – low risk patients (age < 65 years, no stroke risk factors)
    • ASA 325 mg/day
Concomitant Disorder Treatment

- **DM**
  - ~1/3 of HF patients; HF risk in diabetic patients is independent of coronary artery disease & HTN
  - concerns of adverse effects with glitazones, metformin
  - Glitazones: contraindicated in class III & IV HF patients
  - metformin labeling: CI in HF
    - retrospective analysis > 3000 HF patients shows metformin safe
      - decreases mortality & hospitalizations
    - no prospective data
    - monitor volume & renal status
Treatment of Acute Decompensated Heart Failure
Box 1: Proposed causes of acute decompensated heart failure due to left ventricular dysfunction

**Primary cardiac**
- Progressive cardiomyopathy with remodelling
- Acute cardiomyopathy (myocarditis, postpartum cardiomyopathy)
- Myocardial ischemia
- Arrhythmia (tachy- or bradyarrhythmia)
- Valvular dysfunction (stenosis or regurgitation)
- Pericardial syndrome (tamponade, constriction)

**Pressure overload**
- Hypertensive urgency or emergency

**Volume overload**
- Sodium or volume load
- Decreased compliance with diuretics
- Renal dysfunction
- Hepatic dysfunction

**High output**
- Shunt (intra- or extracardiac)
- Anemia
- Septicemia
- Thyroid disease

**Other**
- Inflammation or infection
- Major surgery
- Lack of compliance with heart failure medications
- New medications (excess β-blockade)
- Substance abuse (alcohol, stimulants)
Box 2: Findings in patients with suspected acute decompensated heart failure

- Prior history of heart failure or myocardial injury
- Dyspnea on exertion, orthopnea or paroxysmal nocturnal dyspnea
- Fatigue
- Increasing edema, weight or abdominal girth

**Physical examination**

- Elevated jugular venous pressure
- Peripheral edema or ascites
- Rales, hypoxia or tachypnea
- Tachycardia, arrhythmia
- Diffuse point of maximal intensity
- Ventricular filling gallop (S3)
- Atrial gallop (S4)
- Cool extremities above the hands and feet
- Poor urine output
Box 3: Tests that may help in the diagnosis and treatment of acute decompensated heart failure

- Chest radiography
- Electrocardiography
- Measurement of B-type natriuretic peptide and N-terminal B-type natriuretic peptide levels
- Other laboratory tests (complete blood count, renal function tests, measurement of electrolyte levels, glucose level, transaminase levels, prothrombin time, troponin level, D-dimer level and arterial blood gas pressure, thyroid function tests and urinalysis)
- Transthoracic echocardiography
- Central venous line or pulmonary artery catheter
Treatment

• Goals
  – relieve congestive symptoms
  – optimize volume status
  – treat symptoms of low CO
  – discharge patients on PO drug therapy

• Diuretics, vasodilators, positive inotropic therapy effective
  – must balance against potential toxicities

• Evaluate potential etiologies, precipitating factors
Approximation of cardiac systolic function and cardiac filling pressures in various acute illnesses

- Sepsis / vasodilatory shock
  - Volume
  - Vasopressors
- Normal “Dry and warm”
- Pulmonary edema “Wet and warm”
  - Loop diuretics
  - Nitrates
  - Bilevel or continuous positive airway pressure
  - Nesiritide
  - Ultrafiltration?
- Hypovolemic shock
  - Volume
- Cardiogenic shock
  - Inotropes?
  - Intra-aortic balloon pump or ventricular assist device?
  - “Dry and cold”
  - “Wet and cold”

Cardiac index, L·min⁻¹·m⁻²
- High output
  - Warm extremities, shunting with coexisting low tissue perfusion
- Low output
  - Cool extremities, fatigue, decreased urine output / elevated serum urea

Volume depletion
- Low jugular venous pressure, skin tenting, orthostasis

Pulmonary capillary wedge pressure, mm Hg

Volume overload
- Peripheral edema, ascites, elevated jugular venous pressure, crackles
Various targets for therapies used in the management of acute decompensated heart failure
# Acute Decompensated HF

## Monitoring Recommendations

<table>
<thead>
<tr>
<th>Value</th>
<th>Frequency</th>
<th>Specifics</th>
</tr>
</thead>
</table>
| Weight              | At least daily | Determine after voiding in the morning  
Account for possible increased food intake as a result of improved appetite |
| Fluid intake/output | At least daily | Strict documentation necessary                                                                   |
| Vital signs         | More than daily| Including orthostatic blood pressure                                                                |
| Signs               | At least daily | Edema, acites, pulmonary rales, hepatomegaly, increased jugular venous pressure, hepatojugular reflux, liver tenderness |
| Symptoms            | At least daily | Orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough, dyspnea, fatigue                          |
| Electrolytes        | At least daily | Potassium, magnesium, sodium                                                                       |
| Renal function      | At least daily | Blood urea nitrogen, serum creatinine                                                              |

http://www.accesspharmacy.com
Outcome evaluation of acute HF

Focus on:
1. acute improvement of symptoms and hemodynamics due to intravenous therapies;
2. criteria for a safe discharge from the hospital;
3. optimization of oral therapy.

• Initially, monitor patients for rapid relief of symptoms related to the chief complaint on admission.
  – This includes improvement of dyspnea, oxygenation, fatigue, JVD, and other markers of congestion or distress.
• Monitor for adequate perfusion of vital organs
  – through assessment of mental status, creatinine clearance, liver function tests, and a stable HR between 50 and 100 beats per minute.
• Adequate skin and muscle blood perfusion and normal pH is desirable.
Outcome evaluation of acute HF

- Monitor changes in hemodynamic variables if available.
- Cardiac index should increase, with a goal to maintain it above 2.2 L/minute per square meter.
- Pulmonary capillary wedge pressure should decrease in volume overloaded patients to a goal of less than 18 mm Hg.
- Closely monitor blood pressures and renal function while decreasing preload with diuretics and vasodilators.
- Ensure patients are euvolemic or nearly euvolemic prior to discharge.
- Since oral therapies can both improve symptoms and prolong survival, optimizing outpatient HF management is a priority when preparing a patient for hospital discharge.
- Ensure that the patient’s regimen includes a vasodilator, β-blocker, a diuretic at an adequate dose to maintain euvolemia, and digoxin or aldosterone antagonist if indicated.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Setting</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>Natriuresis (preload reduction)</td>
<td>Volume overload with elevated left and right ventricular filling pressures</td>
<td>Bolus intravenous infusion (dose is often about twice the patient’s usual dose at home); adjust dose based on urine output; add thiazide (metolazone 2.5-5 mg orally daily or chlorothiazide 250-500 mg intravenously once or twice daily), or switch furosemide to a continuous infusion (5-30 mg/h), or both in severe cases with diuretic resistance</td>
<td>Foundation of treatment for acute decompensated heart failure in patients with symptoms of congestion (“wet and warm”)</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Venovenous filter to remove free water</td>
<td>Alternative to loop diuretics for treatment of volume overload</td>
<td>Ultrafiltration/hemofiltration system; fluid removal rates as dictated by clinical assessment, adequate blood pressure and system capabilities</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Venodilation (preload reduction), coronary vasodilator (anti-ischemic)</td>
<td>Volume overload with adequate blood pressure, cardiac ischemia</td>
<td>1-2 sprays of sublingual nitroglycerin (0.3-0.8 mg) every 3-5 min at first. Consider transition to continuous intravenous infusion (v. topical paste): 10-20 µg/min intravenously at first; increase by 5-20 µg/min every 3-5 min as blood pressure allows</td>
<td>Probably underused in patients presenting with acute decompensated heart failure and adequate blood pressure</td>
</tr>
<tr>
<td>Positive pressure ventilation</td>
<td>Positive intrathoracic pressure (preload reduction)</td>
<td>Volume overload with (or without) dyspnea or hypoxia</td>
<td>Continuous positive airway pressure (with or without bilevel positive airway pressure) at pressure of 5-20 cm H₂O</td>
<td>Consider short-term use (hours) in patients with acute decompensated heart failure in acute respiratory distress</td>
</tr>
<tr>
<td>Morphine</td>
<td>Venodilator (preload reduction)</td>
<td>Volume overload with adequate blood pressure <em>after</em> nitroglycerin treatment</td>
<td>Bolus 2-4 mg intravenously</td>
<td>No evidence of efficacy; second-line treatment</td>
</tr>
<tr>
<td>Drug</td>
<td>Mechanism</td>
<td>Indication</td>
<td>Administration</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>Venodilator (preload reduction)</td>
<td>Volume overload with adequate blood pressure</td>
<td>Bolus 2 µg/kg; then infusion 0.01 µg/kg per min, adjusting dose up to 0.03 µg/kg per min</td>
<td>Not currently available in Canada</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Arterial vasodilator (afterload reduction)</td>
<td>Acute heart failure with severe hypertension, or mitral valve regurgitation with adequate blood pressure</td>
<td>Continuous intravenous infusion of 0.3 µg/kg per min at first; titrate rapidly to desired blood pressure; maximum dose 10 µg/kg per min</td>
<td>Use nitroglycerin instead in most patients with acute decompensated heart failure; light sensitive; toxic levels of thiocyanate may accumulate</td>
</tr>
<tr>
<td>Vasodilating inotropes</td>
<td>Inotrope, chronotrope, systemic vasodilator, pulmonary vasodilator</td>
<td>Acute heart failure unresponsive to above therapies, worsening renal function</td>
<td>Dobutamine: 2-20 µg/kg per min intravenously Milrinone: 0.125-0.75 µg/kg per min intravenously (may load 50 µg/kg intravenously over 10 min, but not necessary); renal adjustment necessary</td>
<td>For short-term use in patients with significantly impaired cardiac output; may increase arrhythmia and risk of death; milrinone has longer half-life than the β-agonists</td>
</tr>
<tr>
<td>Vasopressor inotropes*</td>
<td>Inotrope, chronotrope, vasoconstrictor</td>
<td>Shock with inadequate blood pressure (possibly low-dose dopamine in cardiorenal syndrome)</td>
<td>Dopamine: 1-50 µg/kg per min intravenously Norepinephrine: 0.01-0.4 µg/kg per min intravenously</td>
<td>Used in critically ill patients with hypotension; typically avoided in pure heart failure with high systemic vascular resistance, but such resistance may be low in acute decompensated heart failure owing to activation of systemic inflammatory response or total circulatory collapse</td>
</tr>
</tbody>
</table>

*Vasopressin and phenylephrine would not typically be used in acute decompensated heart failure.
Heart failure with preserved left ventricular ejection fraction
Heart failure with preserved left ventricular ejection fraction

- In the absence of more landmark clinical studies, the current treatment approach for diastolic dysfunction or preserved LVEF is:
  1. correction or control of underlying etiologies (including optimal treatment of hypertension and CAD and maintenance of normal sinus rhythm);
  2. Reduction of cardiac filling pressures at rest and during exertion;
  3. increased diastolic filling time.
Heart failure with preserved left ventricular ejection fraction

- Diuretics, ACE inhibitors, and ARBs are frequently used to control congestion.
- Angiotensin receptor blockers may also slow disease progression.
- β-Blockers and calcium channel blockers can theoretically improve ventricular relaxation through negative inotropic and chronotropic effects.
- Unlike in systolic HF, nondihydropyridine calcium channel blockers (diltiazem and verapamil) may be especially useful in improving diastolic function by limiting the availability of calcium that mediates contractility.
- The role of digoxin for symptom management and HR control in these patients is not well established. AHA/ACCF currently DO NOT recommend digoxin in HFprEF.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B (27, 91)</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B (589)</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; COR, Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and LOE, Level of Evidence.
Case Presentation 1

A 60 year old male with non ischemic cardiomyopathy (EF 20%,) presents to clinic (1999) for medication management. S/P recent hospitalization for heart failure, and cardiac catheterization that revealed no significant CAD.

Other PMH: h/o PUD, chronic LBP, HTN, history of NSVT

Symptoms: DOE with 2-4 blocks walking, 1+ BLE stable, no PND, “very fatigued with little activity”—NYHA Class III
Diet: Low salt (< 2gm sodium day), “cautious” with fluids

Vitals: BP 130/80mmHg, pulse 82, Weight 194 lbs
Labs: wnl (Cr 1.2mg/dL (0.5-1.3), K+ 4.5meq/L (4.0-5.2), LDL 110mg/dL
Meds: ASA EC 81mg daily, Lisinopril 5mg daily, Furosemide 40mg daily

Q: What would be reasonable modifications in order to maximize the pharmacologic treatment of this patient’s heart failure?

1) Increase lisinopril?
2) Initiate beta-blocker?
3) Initiate digoxin?
Case Presentation 1

• Increase lisinopril?
  – Based on ATLAS study this would reduce morbidity

• Initiate beta-blocker?
  – Based on MERIT-HF, Carvedilol studies, and others beta, blockers reduce morbidity and mortality in NYHA II-III patients

• Initiate digoxin?
  – Based on DIG Trial this would reduce morbidity
Case Presentation 1

Lisinopril was increased over several weeks to a dose of 40mg daily. Patient returns for follow-up visit with continued complaints of DOE with 6 blocks, fatigue, and bilateral edema (1+). No PND, dizziness or lightheadedness, or orthopnea. Fatigue improved per patient.

Vitals: BP 115/70, pulse 84, Weight 195 (previous 194), Lungs CTA Labs: wnl, Cr 1.4 up from 1.2, K+ 5.4 up from 4.5
Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 40mg daily

Q: What changes should be considered (if any) at this time?
Case Presentation 1

- Decrease lisinopril? (serum creatinine now 1.4 and potassium 5.4)
- Increase furosemide? (patient still SOB with 1+ BLE)
- Initiate beta-blocker? (patient maximized on ACE inhibitor and still symptomatic)
- Initiate digoxin?
Case Presentation 1

• Decrease lisinopril?
  – The slight changes in serum creatinine and potassium manifested by patient do not warrant this

• Increase furosemide?
  – Symptoms are still stable (weight, 1+ edema, SOB) and lungs CTA

• Initiate beta-blocker?
  – Patient maximized on ACE inhibitor and still symptomatic

• Initiate digoxin?
  – May improve symptoms and reduce morbidity
Case Presentation 1

Patient was initiated on carvedilol 3.125mg twice daily and digoxin 0.125mg daily. He returns in 2 weeks with complaints of increased SOB, increased edema, and weight gain. He also complains of dizziness soon after taking his lisinopril and carvedilol.

Vitals: BP 105/60, pulse 78, Weight 199 (baseline 194), Lungs-rales
Labs: wnl, Cr 1.2, K⁺ 5.2, digoxin trough 0.8ng/mL

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 40mg daily, Carvedilol 3.125mg twice daily, Digoxin 0.125mg daily

Q: What should be done at this point?
Case Presentation 1

- Stop carvedilol? (patient not tolerating, BP too low at 105/60 and patient dizzy and lightheaded)
- Increase carvedilol? (higher doses show more benefit)
- Change beta-blockers?
- Increase digoxin? (level only 0.8ng/mL and patient still symptomatic)
- Decrease lisinopril? (BP too low at 105/60 and patient dizzy and lightheaded)
- Increase furosemide? (rales, increased weight & edema)
- Review timing of carvedilol and lisinopril doses
Case Presentation 1

Furosemide was increased to 80mg daily x 3 days, and then return to 40mg qd with 20mg prn weight/edema. Patient instructed to take carvedilol with food and lisinopril 2 hours later.

On return in 1 week patient reports breathing is better, no edema, but still SOB with 6 blocks of walking. No dizziness as long as he takes carvedilol with food and lisinopril 2 hours later. He reports he had to take the 80mg of furosemide daily in order to control weight/edema and SOB.

Vitals: BP 100/65, pulse 78, Weight 195 (baseline 194), Lungs-CTA Labs: wnl, Cr 1.4, K⁺ 5.0

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 80mg daily, Carvedilol 3.125mg twice daily, Digoxin 0.125mg daily

Q: What should be done at this point?
Case Presentation 1

- Stop carvedilol? (BP too low at 100/65)
- Increase carvedilol? (higher doses show more benefit)
- Decrease lisinopril? (BP too low at 105/60)
- Nothing?
Case Presentation 1

As patient had only been “stable” again x 1 week nothing was done. He returned in 2 more weeks and over a period of 2 more months his carvedilol was slowly increased.

Patient presents today feeling “good”. Can walk up to 8 blocks without becoming SOB. Minimal edema. Not as fatigued. However, gets dizzy at times, particularly with quick movements.

Vitals: BP 94/60, pulse 58, Weight 193 (baseline 194), Lungs-CTA
Labs: wnl, Cr 1.6, K⁺ 4.8, Magnesium 2.0

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 80mg daily, Carvedilol 12.5mg twice daily, Digoxin 0.125mg daily

Q: What should be done at this point?
Case Presentation 1

- Reduce carvedilol? (BP too low at 94/60 and pulse 58)
- Increase carvedilol? (higher doses show more benefit)
- Decrease lisinopril? (BP too low at 94/60)
- Decrease furosemide? (BP too low at 94/60 and pt shows signs of over diuresis-creatinine, weight, symptoms)
- Other diagnostic tests? (i.e. EKG, Holter, EPS study)
Case Presentation 1

Diagnostic tests (EKG/Holter) revealed no rhythm disturbances. Furosemide was decreased to 40mg daily with an extra 20mg as needed. Patient returns in 2 weeks with dizziness resolved. No complaints. Can walk up to 8 blocks without becoming SOB. Minimal edema.

Vitals: BP 102/64, pulse 56, Weight 195 (baseline 194), Lungs-CTA
Labs: wnl, Cr 1.3, K⁺ 4.9

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 40mg daily with 20mg as needed, Carvedilol 12.5mg twice daily, Digoxin 0.125mg daily

Q: What should be done at this point?
Case Presentation 1

Nothing was done as it was felt that patient was maximized on carvedilol, and doing well with current vitals, and other medications.
Patient returned for 12 month follow-up feeling “great”. Can walk “around the mall” without becoming SOB. Minimal if any edema. Fatigued only when he “over-exerts” himself.

Vitals: BP 105/66, pulse 58, Weight 194 (baseline 194), Lungs-CTA
Labs: wnl, Cr 1.3, K⁺ 4.5

MUGA: EF 28% up from 20%
NYHA Class I-II

Meds: ASA EC 81mg daily, Lisinopril 40mg daily, Furosemide 40mg daily with 20mg as needed, Carvedilol 12.5mg twice daily, Digoxin 0.125mg daily
Case Presentation 1

At 18 and 24 month follow-up visits patient continues the same with SBP in upper 90’s, pulse mid 50’s and symptoms well controlled.

2 weeks after 36 month follow-up visit you receive call that patient collapsed suddenly in his yard and that resuscitation efforts were unsuccessful.

What happened?
Case Presentation 1 - Conclusions

- Close monitoring required to optimally treat patients
- Patient education and understanding of therapies essential
- Select therapies based on clinical evidence as well as patient presentation/progress
- Medications can improve, but not “cure” heart failure
- Options are continually changing. Patient may have been a candidate for
  - Aldosterone Antagonist (RALES study, 1999)
  - AII blocker (CHARM study, 2003)
  - AICD? (DEFINITE study, 2003)
Distinctive features of ESC guidelines in comparison with AHA/ACCF guidelines

• Nebivolol is a beta-blocker recommended for HF management in the ESC guidelines but not yet in the AHA/ACCF despite studies that showed modest survival benefit in systolic HF patients.

• ESC guidelines: ARBs can be added to ACEIs when patients remains symptomatic despite optimal treatment with ACEI & BRB unless a patient receives aldosterone antagonist. AHA: ARBs are alternatives to ACEIs or can be added only if the patient remains hypertensive despite ACEI, BB and Loop diuretic therapy as long as an aldosterone antagonist is not given to the patient.