Heart Failure and the Primary Care Physician

Delivering the Latest in Evidence-Based Care

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Learning Objectives

• Appropriately evaluate patients with symptoms of new or worsening heart failure
• Tailor treatment plans for heart failure patients based on heart failure classification and evidence-based guidelines
• Identify the correct timing for referral to cardiovascular/heart failure specialists

Heart Failure Defined

A clinical syndrome characterized by the inability of the heart to generate sufficient cardiac output to meet the metabolic demands of the end organs or to do so only with increased cardiac filling pressures.

Definition of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</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>41–49%</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HFREF.</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>
Class I: No limitation
A. No CV disease

Class II: Slight limitation
B. Minimal CV disease

Class III: Marked limitation
C. Moderate CV disease

Class IV: Symptoms at rest
D. Severe CV disease

1. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure. 2001
3. Packer and Cohn, eds. Am J Cardiol. 1999;83(suppl 2A):1A-38A.

High risk with no symptoms

Structural heart disease with no symptoms

Structural heart disease with symptoms (dyspnea, fatigue, reduced exercise tolerance)

Refractory symptoms requiring special interventions

Classification of Heart Failure

The New York Heart Association (NYHA) classification system

STAGE A Heart Failure
At Risk for Heart Failure
At high risk for HF but without structural heart disease or symptoms of HF

- Patients with:
  - hypertension
  - atherosclerotic disease
  - diabetes
  - obesity
  - metabolic syndrome

Therapy Goals
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

Drugs
- ACEI or ARB in appropriate patients with vascular disease or diabetes


STAGE B Heart Failure
At Risk for Heart Failure
Structural heart disease but without signs or symptoms of HF.

- Patients with:
  - previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

Therapy Goals
- All measures under Stage A
- ACEI or ARB in appropriate patients
- Beta-blockers in appropriate patients


STAGE C Heart Failure
Heart Failure
Structural heart disease with prior or current symptoms of HF

- Patients with:
  - known structural heart disease
  - shortness of breath and fatigue, reduced exercise tolerance

Therapy Goals
- All measures under Stages A and B
- Dietary salt restriction
- Diuretics for fluid retention
- ACEI
- Beta-blockers

Drugs
- ACEI
- Beta-blockers


STAGE D Heart Failure
Heart Failure
Refractory HF requiring specialized interventions.

- Patients
  - who have marked symptoms at rest despite maximal medical therapy
  - (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

Therapy Goals
- Appropriate measures under Stages A, B, C
- Decision re: appropriate level of care

Options
- End-of-life care
- Extraordinary measures:
  - Heart transplant
  - Chronic inotropes
  - Permanent mechanical support
  - Experimental surgery or drugs

**Pathophysiology of Heart Failure**

- Cardiac injury
- Increased load
- Activation of RAA System, SNS, and cytokines
- Reduced systemic perfusion
- Altered gene expression
- Growth and remodeling
- Ischemia and energy depletion
- Direct toxicity
- Apoptosis
- Necrosis
- Cell death

RAA = renin-angiotensin-aldosterone
SNS = sympathetic nervous system

Adapted from: Eichhorn EJ, Bristow MR. Circulation. 1996;94:2285-2296.

**Major Therapeutic Options for Heart Failure**

- ACE inhibitor
- Aldosterone receptor blocker
- Angiotensin receptor blocker (if ACE-I intolerant)
- Beta-blocker
- Diuretic
- Digoxin

**Effect of ACE Inhibitors on Mortality in Heart Failure Patients**

<table>
<thead>
<tr>
<th>Trial</th>
<th>ACE-I (%)</th>
<th>Controls (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS I</td>
<td>39</td>
<td>54</td>
<td>0.56 (0.34–0.91)</td>
</tr>
<tr>
<td>SOLVD (Treatment)</td>
<td>35</td>
<td>40</td>
<td>0.82 (0.70–0.97)</td>
</tr>
<tr>
<td>SOLVD (Prevention)</td>
<td>15</td>
<td>16</td>
<td>0.92 (0.79–1.08)</td>
</tr>
<tr>
<td>Post-MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE (captopril)</td>
<td>20</td>
<td>25</td>
<td>0.81 (0.68–0.97)</td>
</tr>
<tr>
<td>AIRE (ramipril)</td>
<td>17</td>
<td>23</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>TRACE (trandolapril)</td>
<td>35</td>
<td>42</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>SMILE (zofenopril)</td>
<td>5</td>
<td>6.5</td>
<td>0.75 (0.45–1.11)</td>
</tr>
<tr>
<td>Totals</td>
<td>21</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>


**Combined All Cause Mortality and Morbidity--ValHeFT**

- 13.3% Risk Reduction
- $P = 0.009$

Cohn JN, et al NEJM 345;1667-1675

**Aldosterone’s Role in Heart Failure**

- ↑ Na⁺
- ↑ LV mass & fibrosis
- ↑ K⁺ & Mg²⁺
- ↓ Cytoskeletal dysfunction
- ↓ Norepinephrine Uptake
- ↓ Heart rate variability
- ↓ Arterial compliance
- ↓ Baroreceptor function
- ↓ Norepinephrine uptake
- ↓ Endothelial function
- ↓ PM-I
- ↑ Edema
- ↑ Remodeling
- ↑ Arrhythmia
- ↑ Ischemic Events
- Progression of HF
- Sudden cardiac death

LV = left ventricular mass

**ACE Inhibitor plus Spironolactone 25 mg/day Further Reduces HF Mortality--RALES**

- Risk reduction 30%
- $P < 0.0001$

Treatment of HF with Low EF
Other RAAS Inhibitors; Beta Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Dose(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone Antagonists</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>Beta-Blockers</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>Metoprolol succinate</td>
<td>12.5 to 25 mg once</td>
<td>500 mg once</td>
</tr>
</tbody>
</table>

ACE inhibitors antagonize angiotensin converting enzyme, mg, metoprol, and spironolactone.

- Eplerenone has a better side effect profile for men but is more expensive
- Selective aldosterone receptor antagonists (SARAs) have minimal diuretic effects at "HF" doses.

Adrenergic Pathway in Heart Failure Progression

- ↑ CNS sympathetic outflow
- ↑ Vascular sympathetic activity
- ↑ Cardiac sympathetic activity
- ↑ Renal sympathetic activity
- Myocyte hypertrophy
- Myocyte injury
- Increased arrhythmias
- Vasoconstriction
- Na retention

Disease progression

RAS = renin-angiotensin system

Effect of Beta-Blockers on Mortality in Heart Failure Patients

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Trial End Point</th>
<th>Risk Reduction, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol</td>
<td>Combined end point: risk of hospitalization or death</td>
<td>35% lower risk (18%-63%) P = 0.001</td>
</tr>
<tr>
<td>CIBIS-II (bisoprolol)</td>
<td>All-cause mortality</td>
<td>34% lower risk P = 0.0001</td>
</tr>
<tr>
<td>MERIT-HF (metoprolol)</td>
<td>All-cause mortality</td>
<td>34% lower risk (0.53-0.81) P = 0.0092 after adjusted interim analysis</td>
</tr>
<tr>
<td>BEST ( bucindolol)</td>
<td>All-cause mortality</td>
<td>8.5% lower risk P = NS</td>
</tr>
<tr>
<td>COPERNICUS (carvedilol)</td>
<td>All-cause mortality</td>
<td>35% lower risk*</td>
</tr>
</tbody>
</table>

Principles of Beta Blocker Therapy

- Start with low doses, but titrate up, Q2-4 wks
- Start in stable patients—decompensation may be delayed, i.e. after discharge
- Medication D/C not usually needed for ADHF admission
  - Yes for shock
  - Down titration occasionally indicated, 50% reduction
- Initiate carefully in hospitalized patients—titration is usually not indicated
- Additive therapy, additive effects
- Usually safe in chronic lung disease except genuine asthma
- Phosphodiesterase inhibitors for inotropy

Treatment of Stage C HF with Low EF
Additional Therapies

Digoxin can be beneficial in patients with HF/EF, unless contraindicated, to decrease hospitalizations for HF.

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 (in the absence of contraindications to anticoagulation).

Effectiveness of Individual Therapies in Preventing Events From Evidence-Based Trials

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Hospital Admissions prevented</th>
<th>Deaths prevented</th>
<th>Evidence-Based Trial / Average Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I</td>
<td>99</td>
<td>13</td>
<td>Treatment arm of the SOLVD trial / 3.5 years</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>65</td>
<td>38</td>
<td>MERIT-HF study / 1 year</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>138</td>
<td>57</td>
<td>RALES trial / 2 years</td>
</tr>
<tr>
<td>Digoxin</td>
<td>40</td>
<td>-</td>
<td>DIG trial / 3 years</td>
</tr>
</tbody>
</table>


HF Preserved Systolic Function (HFpEF)

Differential Diagnosis in Patient with HF and Normal LVEF with Symptoms

- Incorrect diagnosis of HF
- Inaccurate measurement of LVEF
- Primary valvular disease
- Restrictive (infiltrative) cardiomyopathies
- Amyloidosis, sarcoidosis, hemochromatosis
- Pericardial constriction
- Episodic or reversible LV systolic dysfunction
- Severe hypertension, myocardial ischemia
- HF associated with high metabolic demand (high-output states)
- Anemia, thyrotoxicosis, arteriovenous fistulae
- Chronic pulmonary disease with right HF
- Pulmonary hypertension associated with pulmonary vascular disorders
- Atrial myxoma
- Diastolic dysfunction of uncertain origin
- Obesity

Treatment of HFpEF

<table>
<thead>
<tr>
<th>Recommendations</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</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 guideline 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>IIIB</td>
<td>B</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III</td>
<td>No</td>
</tr>
</tbody>
</table>

HFpEF = heart failure with preserved ejection fraction. GDMT = guideline-determined medical therapy. COR = class of recommendation, LOE = level of evidence

Stage C: Nonpharmacological Interventions

- Patients with HF should receive specific education to facilitate HF self-care.
- Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status.
- Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms.

Stage C: Nonpharmacological Interventions (cont.)

- Continuous positive airway pressure (CPAP) can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea.
- Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality.

LVEF = left ventricular ejection fraction
HRQOL = health-related quality of life

Heart Failure Outcomes

Targets and Strategies for Improvement

Quality Metrics/Performance Measures

Performance measures based on professionally developed clinical practice guidelines should be used with the goal of improving quality of care for HF.

Participation in quality improvement programs and patient registries based on nationally endorsed, clinical practice guideline-based quality and performance measures may be beneficial in improving quality of HF care.

Post-Discharge Follow-Up after ADHF

- The post-discharge period is a time of vulnerability
- Early re-evaluation may be crucially important, particularly for higher risk patients
- Affords opportunity for early reassessment, including labs
- Provides a chance for drug review and titration to target doses
- Allows for further education opportunities
- Home telemedicine programs are expanding for higher risk patients and may improve outcome

ADHF = acute decompensated heart failure

Target: HF Optimal Care Transitions Follow-up, and Patient Education

- Discharge use of ACEI/ARB, evidence-based beta blocker, and aldosterone antagonist in all eligible heart failure patients with reduced LVEF, in absence of documented contraindications, intolerance, or patient/system reasons
- Early post-discharge follow-up with visit or phone call scheduled to occur within 7 days of hospital discharge
- F/U outpatient labs for electrolytes, renal function
- Enhanced patient education as evidenced by referral to heart failure disease management program, provision of at least 60 minutes of heart failure education by a qualified heart failure educator, or provision of AHA heart failure interactive workbook
- Consider cardiac rehabilitation

Causes for Elevated Natriuretic Peptide Levels

Cardiac
- Heart failure, including RV syndromes
- Acute coronary syndrome
- Heart muscle disease, including LVH
- Pericardial disease
- Atrial fibrillation
- Myocarditis
- Cardiac surgery
- Cardioversion

Noncardiac
- Advancing age
- Anemia
- Renal failure
- Pulmonary causes: obstructive sleep apnea, severe pneumonia, pulmonary hypertension
- Critical illness
- Bacterial sepsis
- Severe burns
- Toxic-metabolic insults, including cancer chemotherapy and envenomation

RV = right ventricular
LVH = left ventricular hypertrophy

Recommendations for Biomarkers in HF

Clinical Events and Findings Useful for Identifying Patients With Advanced HF

- Repeated (≥2) hospitalizations or emergency department visits for HF in the past year
- Progressive deterioration in renal function (e.g., rise in BUN and creatinine)
- Weight loss without other cause (e.g., cardiac cachexia)
- Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
- Intolerance to beta blockers due to worsening HF or hypotension

BUN = blood urea nitrogen

Adapted from Russell SD et al. Congest Heart Fail. 2008;14:316-21.
Clinical Events and Findings Useful for Identifying Patients With Advanced HF (cont.)

- Frequent systolic blood pressure <90 mm Hg
- Persistent dyspnea with dressing or bathing requiring rest
- Inability to walk 1 block on the level ground due to dyspnea or fatigue
- Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d and/or use of supplemental metolazone therapy
- Progressive decline in serum sodium, usually to <133 mEq/L
- Frequent ICD shocks


Stage D: Therapy

Recommended therapies include:

- Control of fluid retention
- Referral to a HF program for appropriate pts
- Discussion of options for end-of-life care
- Informing re: option to inactivate defibrillator
- Device use in appropriate patients
- Surgical therapy –
  - Cardiac transplantation
  - Mitral valve repair or replacement
- Other
- Drug Therapy –
  - Positive inotrope infusion as palliation in appropriate patients


Inpatient and Transitions of Care

The use of performance improvement systems and/or evidence-based systems of care is recommended in the hospital and early postdischarge outpatient setting to identify appropriate HF patients for GDMT, provide clinicians with useful reminders to advance GDMT, and to assess the clinical response.

GDMT = guideline-determined medical therapy


Inpatient and Transitions of Care

Multidisciplinary HF disease-management programs are recommended for patients at high risk for hospital readmission, to facilitate the implementation of GDMT, to address different barriers to behavioral change, and to reduce the risk of subsequent rehospitalization for HF.

Scheduling an early follow-up visit (within 7 to 14 days) and early telephone follow-up (within 3 days) of hospital discharge is reasonable.

Use of clinical risk prediction tools and/or biomarkers to identify patients at higher risk for postdischarge clinical events is reasonable.

GDMT = guideline-determined medical therapy


Inpatient and Transitions of Care

Throughout the hospitalization as appropriate, before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed:

a. initiation of GDMT if not previously established and not contraindicated;

b. precipitant causes of HF, barriers to optimal care transitions, and limitations in postdischarge support;

c. assessment of volume status and supine/upright hypotension with adjustment of HF therapy, as appropriate;

d. titration and optimization of chronic oral HF therapy;

e. assessment of renal function and electrolytes, where appropriate;

f. assessment and management of comorbid conditions;

g. reinforcement of HF education, self-care, emergency plans, and need for adherence; and

h. consideration for palliative care or hospice care in selected patients.


Conclusions

- Evidence-based guideline directed diagnosis, evaluation and therapy should be the mainstay for all patients with HF.

- Effective implementation of guideline-directed best quality care reduces mortality, improves QOL and preserves health care resources.

- Ongoing research is needed to answer the remaining questions including: prevention, nonpharmacological therapy of HF, including dietary adjustments, treatment of HFpEF, management of hospitalized HF, effective reduction in HF readmissions, more precise use of device-based therapy, smaller MCS platforms and cell-based regenerative therapy.

MCS = mechanical circulatory support
Vignette #1

• 34-year-old male recently diagnosed with dilated cardiomyopathy when presenting to the ED with progressive dyspnea on exertion
• Had been seen twice in your office over the last 6 weeks for dyspnea and cough and completed a course of antibiotics
• Discharged after 2 days of diuresis and started on lisinopril and carvedilol

Vignette #2

• 63-year-old female with chronic ischemic heart disease, diabetes mellitus, and Stage II CKD
• Presents in the office with NYHA Class III symptoms reporting she felt a shock from her ICD this morning
• Has had three hospitalizations this year and during her last hospitalization had both ACEI and beta blocker dosages reduced due to symptomatic hypotension