Heart Failure

Heart failure (HF) is the inability of the heart to pump a sufficient amount of blood to required tissues in a timely manner. HF is a progressive disease in which onset is triggered by the worsening of other concomitant disease states such as coronary artery disease, left ventricular dysfunction and chronic hypertension. Nearly 5 million people in the US are affected by this disease, with 500,000 new cases diagnosed each year.1

The intent of this newsletter is to provide a quick reference of risk factors, assessment and classification guidelines, and treatment overview, along with an Evidence-Based Medicine (EBM) analysis and summarization of recent publications relating to HF drug therapy.

Risk factors for developing HF1,2
- Coronary artery disease
- Chronic hypertension
- Idiopathic dilated cardiomyopathy
- Valvular heart disease
- Sarcoidosis
- Arrhythmia
- Anemia
- Fluid volume overload
- Thyroid disease
- Diabetes Mellitus
- Renal failure
- High salt intake
- Pulmonary embolism
- Medication-induced problems
- Cardiotoxic drug therapy
- Alcohol abuse
- History of Rheumatic fever
- Family history of cardiomyopathy
Signs suggestive of HF
- Bilateral rales
- Third heart sound (S3)
- Laterally displaced apical impulse
- Increased jugular venous pressure
- Tachycardia
- Weight Gain
- Positive hepatojugular reflux
- Peripheral edema not due to venous insufficiency

Symptoms suggestive of HF
- Dyspnea on exertion
- Dyspnea at rest
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Fatigue
- Decreased exercise tolerance
- Unexplained cough, especially at night
- Acute confusional state, delirium
- Decreased food intake
- Decline in functional status
- Nausea, abdominal pain or distention

New Diagnostic Markers

Newer diagnostic markers are being evaluated currently. Studies have shown a relationship between Atrial Natriuretic Peptide (ANP) and HF. In addition, a link between Brain Natriuretic Peptide (BNP) and HF also exists. According to the ACC/AHA Practice Guidelines, a diagnosis of symptomatic HF or ventricular dysfunction would be supported by a BNP level > 100 pg/mL. In addition, recent data suggests plasma homocysteine levels may have some link to the development of HF, but further evaluation is warranted.

Classification Systems

The New York Heart Association (NYHA) classification is the standard classification system for Heart Failure (HF). The American College of Cardiology (ACC) and the American Heart Association (AHA) Task Force have collaboratively developed a broader classification scheme for HF patients, based on the development and succession of the disease. These classifications encompass the spectrum of those patients at risk for developing HF, including patients with severe/end-stage HF.

Table 1: The New York Heart Association Functional Classification of Heart Failure

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No Limitation: ordinary physical exercise does not cause undue fatigue, dyspnea, or palpitations.</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnea.</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms.</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity.</td>
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Table 2: ACC/AHA Classification for Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Patients at high risk for developing HF because of the presence of conditions that are strongly associated with the development of HF. Patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves &amp; have never shown signs or symptoms of HF.</td>
<td>Systemic hypertension; coronary artery disease; diabetes mellitus; history of cardiotoxic drug therapy or alcohol abuse; personal history of rheumatic fever; family history of cardiomyopathy</td>
</tr>
<tr>
<td>B</td>
<td>Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.</td>
<td>Left ventricular hypertrophy or fibrosis; left ventricular dilatation or hypocontractility; asymptomatic valvular heart disease; previous myocardial infarction.</td>
</tr>
<tr>
<td>C</td>
<td>Patients who have current or prior symptoms of HF associated with underlying structural heart disease.</td>
<td>Dyspnea or fatigue due to left ventricular systolic dysfunction; asymptomatic patients who are undergoing treatment for prior symptoms of HF.</td>
</tr>
<tr>
<td>D</td>
<td>Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.</td>
<td>Patients who are frequently hospitalized for HF and cannot be safely discharged from the hospital awaiting heart transplantation; patients at home receiving continuous intravenous support for symptom relief or being supported with a mechanical circulatory assist device; patients in a hospice setting for the management of HF.</td>
</tr>
</tbody>
</table>

Treatment Recommendations

Prevention and treatment of HF begins with the optimal management of other health issues, such as lipids, diabetes, and thyroid disorders, as detailed in Table 2. Non-pharmacologic treatment consists of reduction in dietary salt, alcohol, tobacco and fluid intake. In addition, patients should be advised to limit long travel times, travel to humid and high altitude areas, and sexual activity. Physicians should recommend exercise as appropriate for each individual, weight management and flu/pneumonia vaccinations.1,3

Currently, most pharmacologic guidelines recommend diuretics (usually loops) as first line treatment of volume overload in HF patients. According to current literature, utilization of ACE inhibitors (ACE) as first line therapy followed by the addition of beta-blockers reduces hypertension, improves systolic dysfunction, and improves ejection fraction, resulting in improved morbidity and mortality rates. Digoxin is widely used to treat symptomatic HF. Angiotension receptor blockers (ARBs) are also used in HF treatment as an alternative for patients intolerant to ACE inhibitors.1,3,5 Spironolactone may be utilized for HF patients in NYHA class III and IV, as the Randomized Aldactone Evaluation Study (RALES) demonstrated decreased morbidity and mortality with its use.3

EBM Analysis of Recent Literature

The Valsartan Heart Failure Trial (Val-HeFT) suggests the use of an ARB in the treatment of HF.6 This trial was a large, randomized, placebo-controlled, double-blind, parallel-group trial, with a total of 5010 patients with either NYHA class II, III, or IV HF. The two primary outcome measures were mortality and the combined endpoint of mortality and morbidity, defined as the incidence of hospitalization for heart failure,
treatment with IV inotropics or vasodilators for > 4 hours without hospitalization, and cardiac arrest with resuscitation.

Patients were randomized to either valsartan or placebo, and then stratified by the use or non-use of beta-blocker. Valsartan treated patients were titrated to a 160mg dose, as tolerated. Characteristics of the 2 treatment groups were similar after randomization, including patients stabilized on “background” HF therapy such as diuretics, digoxin, beta-blocker, and ACE inhibitors. No difference was observed in overall mortality in patients treated with valsartan in addition to stabilized ACE inhibitor therapy when compared to placebo.

Mortality results were similar in the two treatment groups. The combined endpoint of mortality and morbidity showed a significant reduction (p = 0.009) in the valsartan group when compared to placebo. The predominant benefit in terms of the combined end point was a 24% reduction in the rate of adjudicated hospitalizations for worsening heart failure as a first event in those receiving valsartan (13.8%) as compared with those receiving placebo (18.2%) (P<0.001). A subgroup analysis of patients treated only with valsartan with no previous exposure to ACE inhibitors or beta-blockers, demonstrated statistically significant improved outcomes in the reduction of mortality when compared to placebo. However, a post hoc subgroup analysis on the 30% of patients on the combination of ACE and beta-blocker therapy at baseline, revealed addition of valsartan therapy increased morbidity and mortality. Clarification of this finding must await the outcome of other ongoing trials evaluating the combination of and ARB with and ACE and beta-blocker. Further evaluation is warranted prior to changing current recommendations.

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) was a large-scale prospective, double-blind, placebo-controlled trial which assessed the effects of metoprolol controlled release (CR)/extended release (XL) on mortality, hospitalization, symptoms, and quality of life in 3991 patients at 313 sites in 14 countries with stable NYHA Class II – IV heart failure. The two primary outcome measures were total mortality and the combined end point of total mortality or all-cause hospitalization (time to first event). The trial was powered appropriately. Patients were started on an initial dosage of one 25mg tablet (one-half tablet if NYHA class III or IV), and dosage was doubled after each 2-week period to target dosage level of 200 mg/d of metoprolol or placebo, and adjusted appropriately with patient response.

An independent safety committee stopped the trial early as an interim preplanned analysis showed a significant 34% reduction in total mortality in the metoprolol CR/XL group. Metoprolol significantly reduced all combined end points (time to first event) compared with placebo. Total mortality or all-cause hospitalizations was reduced by 19%, total mortality or hospitalization for worsening heart failure by 31%, death or heart transplantation by 32%, cardiac death or nonfatal AMI by 39%, and emergency department visit due to worsening heart failure by 32%.

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group conducted a large-scale, prospective, double-blind, placebo-controlled trial to determine the efficacy of carvedilol, a non-selective beta-blocker, in 2289 patients with severe HF. The primary endpoint of this trial was death from any cause, with a combined secondary endpoint of risk of death or hospitalization.

Patients with severe stable chronic HF as a result of ischemic or nonischemic cardiomyopathy were enrolled at 334 centers in 21 countries. Patients were titrated from
an initial 3.125 mg up to a target dose of 25 mg of carvedilol as tolerated. The trial was powered appropriately and designed to continue until 900 deaths had occurred.

An independent data and safety monitoring board stopped the trial early due to the observation of a significant decrease in risk of death [35% (19 to 48%), P=0.0014, 95% Confidence Interval (CI)] observed in patients treated with carvedilol. A significant decrease [24% (11 to 33%), P<0.001, 95% CI] in the combined endpoint of both hospitalization and risk of death was also observed for patients receiving carvedilol. Mean duration of follow-up was 10.4 months. A subgroup analysis for the highest-risk cohort, which included those with recent or recurrent cardiac decompensation or severely depressed cardiac function, carvedilol reduced the risk of death by 39%(11 to 59%), P=0.009, 95% CI, and decreased the combined risk of death or hospitalization by 29%(11 to 44%), P=0.003, 95% CI.

Note: These results apply only to stable NYHA Class IV patients, and do not include those excluded from this study population with unstable severe HF, such patients requiring intensive care, those with marked fluid retention or those receiving IV vasodilators or positive inotropic agents.7

Eplerenone is a new selective aldosterone receptor antagonist (SARA) approved by the FDA in September 2002 for the treatment of hypertension alone or in combination. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial results were published in April, 2003 which assessed the effect of eplerenone on morbidity and mortality among patients with acute myocardial infarction (AMI) complicated by left ventricular dysfunction and heart failure.11 Primary endpoints were time to death from cardiovascular causes or first hospitalization for a cardiovascular event, including heart failure, recurrent AMI, stroke, or ventricular arrhythmia. This multicenter, international, randomized, double-blind, placebo-controlled trial with 6,632 patients 3-14 days post-AMI with left ventricular dysfunction.

During a mean follow-up of 16 months, 478 (14.4%) deaths in the eplerenone group and 554 (16.7%) deaths in the placebo group occurred [relative risk (RR) 0.85; P = 0.008]. The rate of the other primary end point, death from cardiovascular causes or hospitalization for cardiovascular events, was reduced by eplerenone (RR 0.87; P=0.002), as was the secondary end point of death from any cause or any hospitalization (RR 0.92; P=0.02). There was also a reduction in the rate of sudden death from cardiac causes (RR 0.79; P=0.03). Eplerenone may be an alternative in patients with intolerance to spironolactone due to adverse drug event of gynecomastia.3

Other issues regarding HF therapy include gender-based differences and racial differences. A subgroup analysis of patients involved in the Digitalis Investigational Group study were examined.8 In this study a link between rate of death due to any cause and digoxin therapy was observed in women, with an absolute difference of 5.8% (95 % CI, 0.5 to 11.1) when compared to men (p = 0.034, for the interaction). When digoxin treated women were compared with women on placebo, an absolute difference of 4.2% (95% CI, -0.5 to 8.8*) was observed. However, men on digoxin therapy compared to placebo were observed to have an improved outcome in the risk of death due to worsening HF with an absolute difference of -1.6% (95% CI, -4.2 to 1.0*).8 (*Note: These two CIs did cross zero, which indicates non significance.)

This trial does not establish a causal relationship between the use of digoxin and increased mortality for women, but only makes the observation that these differences
may exist. The authors suggest one potential contributing factor to this observation could be interactions between an effect of hormone replacement therapy (HRT) with digoxin. HRT can potentially raise digoxin levels, which could lead to more digoxin-related adverse events in women. Data was not, however, collected to evaluate this issue in this particular study. Further evaluation of this gender-based correlation is warranted prior to changing current recommendations.

In another retrospective analysis of the U.S. Carvedilol Heart Failure Trials Program, the issue of race was studied to determine efficacy in black populations versus non-blacks. Although this study did not show a difference in the efficacy of carvedilol in blacks versus non-blacks, this study did show efficacy of carvedilol for black patients when compared to placebo. This was a positive finding as compared to previous studies that have suggested lack of efficacy in black patients treated with ACE inhibitors and other beta-blockers. Further evaluation of the racial response to drug therapy is required before definite conclusions may be made.9

Trials in Progress

Trials are in progress to determine the efficacy of ARB therapy alone vs. combination therapy with ACE inhibitor.

- The Optimal Therapy in Myocardial Infarction with the All Antagonist Losartan (OPTIMAAL) study comparing Losartan vs. Captopril in post-MI patients.
- The Valsartan in Acute Myocardial Infarction Trial (VALIANT) comparing valsartan vs. captopril vs. combination.
- The Candesartan in Heart Failure to Affect Reduction in Morbidity and Mortality (CHARM) study involving candesartan vs. placebo in CHF patients.10

Conclusion

Many options are available for treatment of heart failure. Treatments are based on symptoms and/or preventative measures. New clinical research findings affect recommendations for optimal treatment of heart failure. Basic goals, however, remain constant: 1) decrease HF symptoms, 2) improve exercise tolerance, 3) improve quality of life, 4) decrease hospitalization and 5) improve morbidity and mortality rates.2 It is important for clinicians to keep up to date on current medical literature findings, keeping in mind drug-drug and drug-disease interactions when prescribing.

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References


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Figure 1: Comparison diagram of the two different classifications of Heart Failure

NHYA Classification

I
No Limitation: ordinary physical exercise does not cause undue fatigue, dyspnea, or palpitations

II
Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnea.

III
Marked limitation of physical activity; comfortable at rest but less than ordinary activity results in symptoms.

IV
Unable to carry out any physical activity without discomfort; symptoms of heart failure are present even at rest with increased discomfort with any physical activity

ACC/AHA Classification

A
Patients at high risk for developing HF because of the presence of conditions that are strongly associated with the development of HF. Patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves & have never shown signs or symptoms of HF.

B
Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.

C
Patients who have current or prior symptoms of HF associated with underlying structural heart disease.

D
Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.


<table>
<thead>
<tr>
<th>Drug Class and Generic Name</th>
<th>Brand Name</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>Bumex</td>
<td>0.5 – 1.0 mg QD to BID</td>
<td>10 mg QD</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Lasix</td>
<td>20 – 40 mg QD to BID</td>
<td>400 mg QD</td>
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<tr>
<td>Ethacrynic acid</td>
<td>Edecrin</td>
<td>25 mg QD</td>
<td>200 mg QD</td>
</tr>
<tr>
<td>Torsemide</td>
<td>Demadex</td>
<td>10 – 20 mg QD to BID</td>
<td>200 mg QD</td>
</tr>
<tr>
<td><strong>Thiazide diuretics</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Hydrochlorothiazide</td>
<td>HydroDiuril</td>
<td>25 mg QD</td>
<td>100 mg QD</td>
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<tr>
<td>Metolazone</td>
<td>Zaroxolyn</td>
<td>2.5 mg QD</td>
<td>10 mg QD</td>
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<tr>
<td><strong>Aldosterone antagonist</strong></td>
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<tr>
<td>Spironolactone</td>
<td>Aldactone</td>
<td>25 mg QD</td>
<td>25 mg QD</td>
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<td><strong>ACE inhibitors</strong></td>
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<tr>
<td>Captopril</td>
<td>Capoten</td>
<td>6.25 mg TID</td>
<td>50 mg TID</td>
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<td>Enalapril</td>
<td>Vasotec</td>
<td>2.5 mg BID</td>
<td>10 – 20 mg BID</td>
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<td>Fosinopril</td>
<td>Monopril</td>
<td>5 – 10 mg QD</td>
<td>40 mg QD</td>
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<td>Lisinopril</td>
<td>Zestril, Prinivil</td>
<td>2.5 mg QD</td>
<td>20 – 40 mg QD</td>
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<td>Quinapril</td>
<td>Accupril</td>
<td>10 mg BID</td>
<td>40 mg BID</td>
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<td>Ramipril</td>
<td>Altace</td>
<td>1.25 mg QD to BID</td>
<td>10 mg QD</td>
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<td>Trandolapril</td>
<td>Mavik</td>
<td>1 mg QD</td>
<td>4 mg QD</td>
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<td><strong>Beta-receptor blockers</strong></td>
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<td>Bisoprolol</td>
<td>Zebeta</td>
<td>1.25 mg QD</td>
<td>10 mg QD</td>
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<tr>
<td>Carvedilol</td>
<td>Coreg</td>
<td>3.125 mg BID</td>
<td>25 – 50 mg QD</td>
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<td>Metoprolol tartrate</td>
<td>Lopressor</td>
<td>6.25 mg BID</td>
<td>75 mg BID</td>
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<tr>
<td>Metoprolol succinate ext. release</td>
<td>Toprol XL</td>
<td>12.5 – 25 mg QD</td>
<td>200 mg QD</td>
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<tr>
<td><strong>Digitalis glycosides</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Lanoxin</td>
<td>0.125 – 0.25 mg QD</td>
<td>0.375 mg QD</td>
</tr>
</tbody>
</table>
Figure 2: An adapted algorithm from the ACC/AHA Practice Guidelines 2001 compared to NYHA

**Stage A**
Patients at high risk for developing HF

**Therapy**
- Treat co-morbid conditions listed as risk factors
- ACE inhibitor therapy as appropriate
- Dietary changes
- Exercise

**Stage B**
Asymptomatic patients with structural heart damage

**Therapy**
- All measures under Stage A
- ACE inhibitor therapy as appropriate
- Beta-blockers as appropriate

**Stage C**
Structural heart damage and symptomatic patients with HF

**Therapy**
- All measures under stage A
- Drugs for routine use: Diuretics, ACE inhibitors, Beta-blockers, Digitalis
- Dietary salt restrictions

**Stage D**
Refractory HF patients requiring specialized interventions

**Therapy**
- All measures under stages A, B, and C
- Mechanical assist devices
- Heart transplantation
- Continuous IV inotropic infusions for palliation
- Hospital Care

**ACC/AHA Practice Guidelines 2001 algorithm**

**NYHA Treatment Guidelines**

This figure allows you to see the similarities and differences in the ACC/AHA treatment algorithm in comparison to the NYHA treatment guidelines.