

Controlling Heart Failure and Improving Clinical Outcome

Heart failure affects more than 5 million Americans, with more than 550,000 new cases occurring annually and a resultant 1,100,000 hospitalizations, which translates into an annual estimated cost of over \$33 billion dollars. Mortality with this condition is high, approximately 50% at 5 years. Implementation of the advances in management of heart failure have the potential to improve patients' quality of life, reduce the need for hospitalizations, reduce total medical costs, and prolong survival.

The approach to diagnosis and management of heart failure (HF) and the goals of therapy are outlined below.

I. Definition

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema.

II. Etiology

Common	Coronary Artery Disease Hypertensive Heart Disease Idiopathic Dilated Cardiomyopathy Valvular Heart Disease Drugs - Alcohol, Cocaine, Methamphetamine HF with Preserved Systolic Function (Diastolic Dysfunction)
Less Common	Congenital Heart Disease Infiltrative Cardiomyopathy - Amyloid, Sarcoid, Restrictive Hemochromatosis Thyroid Disease Pheochromocytoma Chronic Kidney Disease HIV and Viral Cardiomyopathy

III. History and Physical Evaluation

Assess and document symptom and functional status (NYHA functional class)
Measure and document orthostatic vital signs. Evaluate for symptoms/signs of volume excess and/or low cardiac output

	<u>Volume Excess</u>	<u>Low Cardiac Output</u>
History	Decreased Exercise Tolerance SOB, DOE Orthopnea, PND Edema Weight Gain RUQ tenderness	Decreased Exercise Tolerance Fatigue Malaise Decreased Appetite Weight Loss
PE	Rales (not always present) Increased JVP Hepatojugular Reflex/tenderness Edema S3	Cachexia Narrow Pulse Pressure Cool Extremities Tachycardia S3

IV. Evaluation of HF

All patients with HF should have initial assessment of left ventricular ejection fraction (echocardiogram). LVEF must be documented in medical record. Assess for precipitating causes and major cardiovascular and non-cardiovascular co-morbidities.

Laboratory	Electrolytes, BUN, Creatinine – assess renal function CBC – assess for anemia T4, TSH - exclude thyroid disease Liver Function Tests - evaluate for right heart failure Cholesterol panel (LDL) - evaluate risk for CAD, risk, and need for statin Urinalysis - exclude nephrotic syndrome
Diagnostic Tests	ECG – prior infarct, LVH, arrhythmias CXR BNP (level < 100 pg/mL makes HF diagnosis unlikely) (also provides important information regarding prognosis) Cardiac troponin: evaluate for ACS and/or ongoing myocardial cellular injury Echocardiography - <u>all patients should have assessment of LV function:</u> quantify LV size, evaluate hemodynamics, diastolic function, valvular heart disease, CAD, amyloid
Additional Tests	If at risk/suspected CAD (angina/MI/risk factors - ETT Nuclear Imaging PET scan or coronary angiogram) CPX - (Cardiopulmonary exercise test) Select patients quantify functional capacity, assess prognosis, guide exercise prescription

Hospitalize for initial management or during follow-up for

- Hypoxia - $O_2 < 90\%$
- Pulmonary edema/anasarca/pneumonia
- Symptomatic hypotension (SBP < 80 mmHg) with significant volume overload
- Inadequate social support in the setting of decompensation of HF refractory to outpatient Rx
- Increasing renal dysfunction not due to overdiuresis; hepatic dysfunction
- Suspicion of low cardiac output status with low SBP

V. Medication for HF - Systolic Dysfunction

Neurohumoral antagonism is the cornerstone of heart failure management. Because of their beneficial effects on disease progression, functional status, hospitalizations, and mortality risk, ACE inhibitor, beta blocker and aldosterone antagonist therapy should be prescribed for all patients with left ventricular systolic dysfunction, unless specific well defined contraindications exist.

Antagonism of Neurohumoral Activation

ACE Inhibitors: Improve survival (17-37% mortality reduction) in patients with Class I-IV heart failure, asymptomatic LV dysfunction, myocardial infarction, hypertension, coronary artery disease, and diabetes. Additional benefits include reduced hospitalization, myocardial infarction, strokes, renal failure, and new onset diabetes.

Doses of ACE inhibitors should be titrated upward over time with the goal of reaching the target doses used in the prospective randomized clinical trials to reduce mortality. Monitor serum K⁺, BUN, Cr at least one week after initiation or dose change and periodically thereafter, earlier if significant renal dysfunction. HF patients with severe renal insufficiency and those on dialysis should be treated with ACE inhibitors. Contraindications: cardiogenic shock, angioneurotic edema, hyperkalemia and pregnancy. Renal insufficiency is a double indication, not a contraindication.

Use Target (Survival) Doses.

	<u>Initiation</u>	<u>Target</u>	<u>Maximum</u>
Enalapril	5 mg bid	10 mg bid	20 mg bid
Lisinopril	10 mg daily	20 mg daily	40 mg daily
Captopril	25 mg tid	50 mg tid	100 mg qid
Quinapril	10 mg bid	20mg bid	40 mg bid
Benazepril	10 mg daily	40 mg daily	80 mg daily
Ramipril	5 mg daily	10 mg daily	20 mg daily

Beta Blockers: Improve survival (34-65% mortality reduction) in patients with Class I-IV heart failure, asymptomatic LV dysfunction, myocardial infarction, hypertension, coronary artery disease, and diabetes. Additional benefits include reduced hospitalization, MI, and sudden death.

Beta blockers should be initiated in all compensated heart failure patients, without contraindications as soon as possible. Patients requiring intravenous inotropic agents should have beta blocker therapy deferred until stabilized. Contraindications: cardiogenic shock, symptomatic bradycardia, 2nd or 3rd degree heart block without pacemaker, reactive airway disease. Note that diabetes, peripheral vascular disease, asymptomatic bradycardia, and COPD are not contraindications. Monitor patients for symptomatic hypotension or symptomatic bradycardia.

Start at low dose with careful titration. Increase at intervals of at least 2 weeks until target dose. The ACC/AHA guidelines recommend using only those beta blockers and those doses that have been proven to reduce mortality (i.e. mortality reduction is not a class effect). COMET demonstrated that carvedilol (beta-1, beta-2, and alpha-1 blockade) provided a 17% mortality reduction compared to beta-1 selective blockade with metoprolol tartrate.

	<u>Initiation</u>	<u>Titration</u>	<u>Target</u>
Carvedilol (preferred)	3.125 mg bid.	6.25, 12.5 mg bid	25 mg bid
Carvedilol CR (preferred)	10 mg daily	20 mg, 40 mg daily	80 mg daily
Metoprolol XL	12.5 mg daily	25, 50, 100, 150 mg daily	200 mg daily
Bisoprolol	1.25 mg daily	2.5, 5 mg daily	10 mg daily

The COPERNICUS trial demonstrates survival benefits with carvedilol in patients with class IV heart failure and that therapy can be initiated during hospitalization. IMPACT-HF demonstrates that in-hospital initiation is safe and improves treatment rates. Strongly consider initiation of carvedilol or switching from other beta blocker to carvedilol prior to heart failure hospital discharge, as this has been shown to improve patient compliance and treatment utilization. For patients who are tenuous or who have failed a prior attempt at beta blocker initiation, ultra low doses may facilitate initiation. One suggested regimen is to initiate Carvedilol 3.125, half tab PO qhs (i.e. 1.5625mg). After one week, the dose is given bid, after 3 more weeks, the patient is advanced to 3.125 mg bid, then slowly titrated up from that level at 4-8 week intervals.

Aldosterone Antagonism: Improve survival (15-30% mortality reduction) in patients with moderately severe to severe HF as well as patients with mild HF post MI. Reduction in hospitalizations and sudden death also demonstrated. Indicated for patients with systolic HF and post MI LVD when close monitoring can be assured. Contraindicated if hyperkalemia or serum Cr > 2.5 mg/dL in men or Cr > 2.0 mg/dL in women

Aldosterone antagonists are administered in conjunction with ACE inhibitors, beta blockers, and frequently loop diuretics. Since these agents are potassium sparing diuretics, patients will likely require adjustment of potassium supplements, possible alteration in other diuretic dosing, and close monitoring of renal function and serum potassium levels. It is recommended that the dose of potassium supplements be reduced on initiation, check K⁺, BUN, Cr at 72 hours, 1 week, and 4 weeks. After adjustments at 4 weeks, increase dose to target level, rechecking labs at 1 week and 4 weeks. .

	<u>Initiation</u>	<u>Target</u>	<u>Maximum</u>
Spirolactone	6.25 or 12.5 mg daily	25 mg daily	25 mg daily
Eplerenone	12.5 or 25 mg daily	50 mg daily	50 mg daily

Angiotensin Receptor Antagonists: CHARM demonstrated benefits of ARB in ACE intolerant patients as well as in patients on ACE inhibitors. Recommend use in patients that cannot tolerate or have unacceptable side effects with ACE inhibitors. Consider as add on therapy to ACE inhibitor and beta blocker in select patients not candidates for aldosterone antagonists.

	<u>Initiate</u>	<u>Target</u>	<u>Maximum</u>
Valsartan	40 mg bid	80-160 mg bid	160 mg bid
Candesartan	8 mg daily	32 mg daily	32 mg daily

Hydralazine/Nitrates: The combination of hydralazine with isosorbide dinitrate reduced mortality by 43% in African Americans with Class III heart failure when added to standard care. These agents work as nitric oxide (NO) donors. The therapeutic role of these agents in HF patients other than African Americans should be further evaluated, but this represents a reasonable option for all HF patients who remain Class III or IV, irrespective of race or ethnicity.

Fixed dose combination Hydralazine 37.5 mg/Isosorbide dinitrate 20 mg 1 to 2 tablets tid

Omega-3 Fatty Acid Supplementation: GISSI-HF demonstrated a 9% relative risk reduction in mortality with 1 gram daily supplementation of omega-3 fatty acids (850-900 mg of EPA/DHA) incremental to other standard of care therapies and irrespective of HF etiology.

Symptomatic Treatments

Digoxin no benefit, no harm on HF mortality, decreases need for HF hospitalizations, but not overall hosp. Use for afib rate control only (keep levels < 1.0 ng/mL)

Diuretics Loop diuretics with potassium supplementation
Flexible regimen with doubled dose for 2 lb weight gain and prn metolazone

Co-morbidities and Related Risks

The majority of heart failure patients (60-70%) have CAD, other atherosclerotic vascular disease, and/or diabetes. They should receive comprehensive atherosclerosis treatment which includes aspirin, beta blocker, ACE inhibitor and statin titrated to an LDL < 70 mg/dL in conjunction with diet, omega-3 fatty acid supplementation, and exercise counseling.

Control of hypertension is also believed to be important, but optimal targets for SBP or DBP have not been established in HF patients. For patients remaining hypertensive despite ACE inhibitor, beta blocker, and aldosterone antagonist, recommend hydralazine/nitrates or alternately amlodipine or doxazocin.

Gold standard evidence-based, guideline-Class I recommended medical therapy to decrease symptoms, reduce hospitalizations, and improve survival in heart failure is now treatment with ACE inhibitor, beta blocker, aldosterone antagonist, and omega-3 fatty acid supplementation. Hydralazine/nitrate combination therapy has also been demonstrated to reduce mortality in black patients.

VI. Medication for HF with Preserved Systolic Function

Although there are not randomized clinical trials available to guide therapy for patients with heart failure and preserved systolic function these patients have similar etiologies, neurohumoral activation, functional impairment, and hemodynamics as patients with systolic dysfunction heart failure. Some but not all observational studies have suggested that ACE inhibitor and beta blocker use is associated with reduced morbidity and mortality in patients with heart failure and preserved systolic function. In addition, these patients frequently have comorbid conditions such as hypertension, coronary artery disease, and/or diabetes where ACE inhibitors and beta blockers are of proven benefit.

It is recommended based on pathophysiology, observational data, and expert opinion that patients with heart failure and preserved systolic function be considered for a similar medical regimen recommended for heart failure with systolic dysfunction (ie ACE inhibitor, beta blocker, potentially aldosterone antagonist, and omega-3 fatty acid supplementation).

VII. Device Therapy for HF

LVEF \leq 0.35, Class II / III, all HF etiologies, ICD therapy reduces mortality by 23% (SCD-HeFT)

LVEF \leq 0.30, post MI: prophylactic ICD therapy indicated, reduces mortality by 31% (MADIT II)
Wait > 40 day after acute myocardial infarction before implanting ICD (DINAMIT)

QRS \geq 120 ms, LVEF \leq 0.35, NYHA III or IV: Cardiac resynchronization therapy with or without ICD indicated, reduces mortality by 36% (COMPANION, CARE-HF)

Prophylactic Placement of an ICD device (with or without CRT) is recommended in conjunction with optimal medical treatment in all eligible HF patients with LVEF \leq 35% on chronic optimal medical therapy without contraindications, as part of standard management. Education and counseling of patients prior to device placement is essential.

VIII. Specific Clinical Scenarios

Volume Excess

ACEI
Beta Blocker
Aldosterone Antagonist
Loop Diuretic

Low Output

ACEI
Digoxin
Aldosterone Antagonist
Hydralazine/Isordil

CAD/CVD/PVD

ASA
Statin
ACEI
Beta Blocker
Omega 3 FA

Tachy Arrhythmias

Atrial fibrillation - Amiodarone
Asymptomatic PVC - Beta Blockers
NSVT and CAD - EPS, if induce, ICD
Syncope, VT, or Sudden Death – ICD

Brady Arrhythmias

D/C Digoxin
Pacemaker - in NSR – consider CRT
in Afib – consider CRT

Indications for anticoagulation: paroxysmal or chronic atrial fibrillation, left ventricular thrombus, or prior systemic embolization. INR 2.0 - 3.0

IX. Medications to Avoid:

Type I Antiarrhythmic Agents	Increase risk of sudden death and mortality 3-4X
Calcium Channel Blockers	Increase risk of HF admit, progressive ventricular dilation, and mortality
NSAIDS and COX-2 inhibitors	Increase risk of renal dysfunction/failure

X. Comprehensive Management

Non Pharmacologic Therapies: Essential Components of Therapy

Diet: 2 gram sodium diet with detailed education of patient and family members
Fluid Restriction: 2 liter (64 oz) daily fluid restriction, if congestive symptoms
Daily Weights: monitor and record daily weights, bring chart to each visit
Flexible Diuretics: Patient centered diuretic dosing, double for 2 lb wt gain, prn metolazone
Daily aerobic exercise: Progressive walking program
Patient Education: detailed patient and family member education with frequent reinforcement
Comprehensive management combining optimization of heart failure medications and patient education can prevent up to 85% of heart failure hospitalizations and reduce total medical costs substantially.

XI. Management of Refractory Patients - Tailored Therapy

Patients with severe decompensated HF and those that have failed empiric therapy may potentially benefit from heart failure program referral. Potential indications for hemodynamic monitoring include:

- Increasing renal or hepatic dysfunction not due to overdiuresis
- Hypotension (SBP < 80 mm Hg) with volume excess (increased JVP)
- Suspicion of low cardiac output status with low SBP (cardiac cachexia)
- Failing to respond to clinically guided dosing of ACEI inhibitor, beta blocker, and diuretic therapy

Decompensated patients are admitted and right heart catheter is placed. Intravenous nesiritide or nitroprusside and diuretics are titrated. Peripheral ultrafiltration may be utilized. Once optimal hemodynamics are achieved, ACE inhibition is started and the dose advanced while weaning the IV vasodilator. Beta blockers then initiated.

Patients who remain symptomatic despite aggressive medical therapy should be referred to a heart transplantation center for evaluation for orthotopic heart transplantation. Patients with advanced heart failure undergoing orthotopic heart transplantation currently have an expected 85-90% 1 year and a 70-75% 5 year survival. Selective patients age 65-70 (with additional risk factors) and those patients age 70 to 74 can be considered for UCLA alternative heart transplantation program.

Implantable LV ventricular assist devices are available to mechanically bridge patients to cardiac transplantation. Studies to evaluate mechanical LV assist devices as long term HF treatment without transplantation have been completed and show some benefit. Other experimental therapies such as cell transfer and stem cell transplantation are also undergoing further evaluation.

XII. Prevention of Heart Failure

Primary Prevention Stage A (prevent development of left ventricular dysfunction)

- Treat Hypertension, especially systolic hypertension (ACEI, beta blocker)
- Treat Hypercholesterolemia (statin, aspirin)
- Treat Atherosclerosis (aspirin, beta blocker, ACEI, statin)
- Treat Diabetes (aspirin, beta blocker, ACEI, statin, glycemic control)
- Weight Loss for Obese Individuals
- Smoking Cessation

Secondary Prevention Stage B (prevent progression from asymptomatic LV dysfunction)

- ACE Inhibitors
- Beta Blockers
- Aldosterone Antagonist post MI LVD
- Secondary Prevention after Myocardial Infraction
(Aspirin, Beta Blocker, ACE inhibitor, Aldosterone Antagonist if LVD, Statin, Exercise)
- ICD (selected indications)

Tertiary Prevention Stage C/D (prevent progression of clinical HF to mortality)

- ACE Inhibitors
- Beta Blockers
- Aldosterone Antagonist
- Omega -3 Fatty Acid Supplementation
- Hydralazine/Nitrate (selected indications)
- Secondary Prevention of Coronary Artery Disease
- ICD and/or Cardiac Resynchronization (selected indications)
- Exercise

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