Managing Heart Failure and Improving Clinical Outcomes

Heart failure (HF) affects over 6 million patients in the US, with 1 million new cases occurring annually and a resultant 900,000 hospitalizations with a primary discharge diagnosis, which translates into an annual estimated cost of over $30 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 HF and the goals of therapy are outlined below.

I. Definition

Heart failure 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 Diabetes Mellitus Idiopathic Dilated Cardiomyopathy Valvular Heart Disease Drugs - Alcohol, Cocaine, Methamphetamine HF with Preserved Ejection Fraction (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.

	Volume Excess	Low Cardiac Output
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 Heart Failure Patients

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, Na, K, Mg
CBC – assess for anemia
TSH - exclude thyroid disease
Liver Function Tests - evaluate for right heart failure
Cholesterol panel (LDL) - evaluate risk for CAD, risk
Urinalysis - exclude nephrotic syndrome

Diagnostic Tests
ECG – prior infarct, LVH, arrhythmias, document QRS duration
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 - all patients should have assessment of LV function: 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, CT angiogram, or coronary angiogram)
CPX - (Cardiopulmonary exercise test) Select patients quantify functional capacity, access prognosis, and guide exercise prescription in select patients
Cardiac MRI, endomyocardial biopsy, or other testing in select patients
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 or low output
Inadequate social support in the setting of decompensation of HF
Refractory to outpatient Rx
Increasing renal dysfunction not due to over diuresis; hepatic dysfunction

V. Medication for Heart Failure and Reduced LVEF (HFrEF, Systolic Dysfunction)

Neurohumoral antagonism is the cornerstone of HFrEF management. Because of their beneficial effects on disease progression, functional status, hospitalizations, and mortality risk, Angiotensin Receptor Neprilysin Inhibitor (ARNI) or ACE inhibitor or ARB, beta-blocker, aldosterone antagonist, and sodium glucose cotransporter 2 (SGLT2) inhibitor therapy should be prescribed for all HFrEF patients, unless specific well-defined contraindications exist.

Antagonism of Neurohumoral Activation

ACE Inhibitors: Improve survival (17-25% mortality reduction) in patients with Class I-IV HFrEF patients as well as in patients with asymptomatic LV dysfunction. Additional benefits include improved functional status, reduced hospitalization, and less myocardial infarction, strokes, and renal failure.

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 still be treated with ACE inhibitors. Contraindications: cardiogenic shock, angioedema, hyperkalemia and pregnancy. Renal insufficiency is a double indication, not a contraindication.

Up-titrate to target dose, or if not well tolerated, highest dose short of that, which is well tolerated.

	Initiation	Target	Maximum
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

Angiotensin Receptor Antagonists: CHARM demonstrated benefits of ARB in ACE intolerant patients. Recommend use in HFrEF patients that cannot tolerate or have unacceptable side effects with ARNI or ACEI. ARB should not be prescribed together with ACEI or ARNI.

	Initiate	Target	Maximum
Losartan	50 mg daily	150 mg daily	150 mg daily
Valsartan	40 mg bid	80-160 mg bid	160 mg bid
Candesartan	8 mg daily	32 mg daily	32 mg daily

Angiotensin Receptor Neprilysin Inhibitor (ARNI): The medication sacubritil/valsartan was shown to reduce the combination of cardiovascular death and heart failure hospitalization in HFrEF patients compared to enalapril by 20%, with an incremental 16% reduction in all-cause mortality. Patients should have SBP >90 mmHg. This agent should be considered first line and preferable to ACEI or ARB therapy, in HFrEF patients who are eligible and can tolerate Rx. Patients who remain NYHA II-III with EF ≤ 40% despite ACEI or ARB should be switched to ARNI. Contraindications include cardiogenic shock, angioedema, hyperkalemia, and pregnancy. Must be off ACEI therapy for 36 hours and do not use ARNI together with either ACEI or ARB. Up-titrate to target dose, or if not well tolerated, highest dose short of that, which is well tolerated.

	Initiation	Target	Maximum
Sacubitril/Valsartan	49/51 mg bid	97/103 mg bid	97/103 mg bid

Start 24/26 mg bid if not previously treated with ACEI/ARB or receiving <full doses.

Beta Blockers: Improve survival (34-65% mortality reduction) in patients with Class I-IV heart failure and reduced LVEF and those with asymptomatic LV dysfunction. Additional benefits include improved LVEF, reduced hospitalization, and reduced risk of MI and sudden death.

Beta-blockers should be initiated in all compensated HF 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, severe 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 2 weeks until target dose. The ACC/AHA guidelines recommend using only one of the 3 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.

	Initiation	Titration	Target
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 Succinate 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. Initiate carvedilol or switching from other beta-blocker to carvedilol prior to HF hospital discharge. 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 mild, moderate, or severe HF and reduced LVEF, as well as in patients with post MI LVD. Reduction in hospitalizations and sudden death also demonstrated. Therapy indicated for patients with HF and reduced LVEF and those with 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 (eGFR <30)

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 loop diuretic dosing, and close monitoring of renal function and 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.

Start at low dose and critical to closely monitor potassium level and renal function

	Initiation	Target	Maximum
Spironolactone	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

SGLT2 Inhibitors: The SGLT2 inhibitors dapagliflozin and empagliflozin were shown to reduce CV hospitalizations and HF events in patients with Class II-IV HFrEF with or without type II diabetes when added to standard care. The benefits were additive to other recommended HFrEF medications. It is not yet know if these agents improve outcome in HFpEF. Avoid in type 1 diabetes.

Dapagliflozin	10 mg daily
Empagliflozin	10 mg daily

Hydralazine/Nitrates: The combination of hydralazine with isosorbide dinitrate reduced mortality by 43% in African Americans with Class III-IV heart failure when added to standard care. These agents may work as nitric oxide (NO) donors. This therapy is recommended in all black HF patients with reduced LVEF, in conjunction with other evidence-based HF medications. The therapeutic role of these agents in HF patients other than African Americans should be further evaluated, but this represents a potential option for HF patients who remain Class III or IV of other races or ethnicity.

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

Ivabradine: This heart rate lowering medication has been shown to lower the risk of HF hospitalization in HFrEF patients in sinus rhythm with resting heart rate of 70 or higher. Consider use in these patients so long as beta-blocker therapy has been maximally titrated as tolerated. Starting dose is five mg bid, and can be titrated up to 7.5 mg bid or down to 2.5 mg bid, depending on heart rate response.

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. May use for afib rate control (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, and statin titrated to an LDL < 70 mg/dL in conjunction with diet/exercise.

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 ACEI or ARB or ARNI, beta-blocker, and aldosterone antagonist, recommend hydralazine/nitrates or alternately amlodipine or doxazosin.

Gold standard evidence-based, guideline-Class I recommended medical therapy to decrease symptoms, reduce hospitalizations, and improve survival in heart failure and reduced LFEF is treatment with ARNI, beta-blocker, aldosterone antagonist.

VI. Medication for Heart Failure with Preserved LVEF (Diastolic Dysfunction)

Although there are not randomized clinical trials showing mortality reduction available to guide therapy for patients with HF and preserved EF, these patients have similar etiologies, neurohumoral activation, functional impairment, and hemodynamics as patients with reduced EF HF. Aldosterone antagonists, ARB, or ARNI may be considered to reduce risk of HF hospitalization. These patients frequently have comorbid conditions such as hypertension, coronary artery disease, and/or diabetes where ACE inhibitors and beta-blockers are of potential benefit.

VII. Device Therapy for Heart Failure and Reduced LVEF

ICD: LVEF $\leq$ 0.35, Class II / III, all HF etiologies, primary prevention ICD reduces mortality by 23% (SCD-HeFT). Chronic optimal medical therapy for > 3 months, >40 day post AMI.

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

CRT: QRS $\geq$ 120 ms, LVEF $\leq$ 0.35, NYHA II to IV: Cardiac resynchronization therapy with or without ICD indicated, reduces mortality by 27-36% (COMPANION, CARE-HF, RAFT). For Class II patients, indications also include LVEF $\leq$ 0.30, QRS $\geq$ 150 ms, LBBB morphology.

Device placement (CRT and/or ICD) is recommended in conjunction with chronic optimal medical treatment in eligible HF patients (meeting all evidence-based criteria without contraindications) as part of standard management. Education and counseling of patients prior to and after device placement is essential.

VIII. Specific Clinical Scenarios

Volume Excess	Low Output	CAD/CVD/PVD
ARNI	ACEI or ARNI	ASA
Beta Blocker	Digoxin	Statin
Aldosterone Antagonist	Aldosterone Antagonist	ARNI
SGLT2 inhibitor	Hydralazine/Isordil	Beta Blocker
Loop Diuretic		Omega 3 FA

Tachy Arrhythmias	Brady Arrhythmias
Atrial fibrillation - Anticoagulation	D/C Digoxin
Asymptomatic PVC - Beta Blockers	Pacemaker - in NSR – consider CRT
Syncope, VT, or Sudden Death – ICD	in Afib – consider CRT

Indications for anticoagulation: paroxysmal or chronic atrial fibrillation, left ventricular thrombus, or prior systemic embolization. INR 2.0 - 3.0 or novel oral anticoagulant (DTI, Factor Xa inhibitor)

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: Sodium restricted diet with detailed education of patient and family members, if congestion
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 disease management combining optimization of HF medications/devices and patient education can prevent up to 85% of HF 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 HF program referral. Potential indications for hemodynamic monitoring include:

Increasing renal or hepatic dysfunction not due to over diuresis
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 nitroprusside, nitroglycerine, or nesiritide and diuretics are titrated. Peripheral ultrafiltration may be utilized. Once optimal hemodynamics are achieved, ACE inhibition, ARB, or ARNI is started and the dose advanced while weaning the IV vasodilator. Beta-blocker then initiated.

Patients who remain symptomatic despite aggressive medical therapy should be referred to a heart transplantation center for evaluation for orthotopic heart transplantation or VAD. Patients with advanced HF undergoing orthotopic heart transplantation currently have an expected 85-92% 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 or as destination therapy. Studies to evaluate mechanical LV assist devices as long-term HF treatment without transplantation have been completed and show benefit.

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, SGLT2 inhibitor)
- 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)
- ARNI
- Beta Blockers
- Aldosterone Antagonist
- SGLT2 Inhibitor
- 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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