REVIEW ARTICLE

Congestive Heart Failure in Adults

Lucia Szabo, DO and Natasha Bray, DO
Broward Health Medical Center, Fort Lauderdale, Florida

KEYWORDS:

Heart Failure

Syndrome of Heart Failure

Cardiomyopathy

Heart Failure with Reduced Ejection Fraction

Heart failure is a clinical syndrome that can challenge the primary care physician when other comorbidities are present. Heart failure diagnosis and treatment options are continuously improved by evidenced based medicine. This review article addresses diagnosis and treatment based on the functional classification of heart failure.

INTRODUCTION

Heart failure (HF) is the leading cause of death in the United States. Although the American Heart Association reports that the death rate has decreased for the past few years, there is still a significant number of deaths secondary to heart failure. The first conclusions on risk factors for heart disease were drawn from the Framingham heart study that included 5,209 males from the ages of 30 to 62 from Framingham, Massachusetts. These patients underwent physical exams and lifestyle modifications as a basis for the data. The study later included multiple cohort generations to identify cardiovascular risk factors determined to be important for heart health such as blood pressure, smoking, obesity, diabetes and lack of exercise. More recent studies indicate that heart failure may be due to comorbidities such as chronic obstructive diseases (COPD), obesity, diabetes mellitus (DM), hypertension (HTN) or psychiatric disorders.[1] Studies have shown that there was a risk for increased readmission rates and mortality in patients with coronary artery disease and heart failure; although mortality rates were slightly higher in patients with diastolic heart failure. In patients with systolic heart failure, increased mortality appears to be associated with presence of diabetes mellitus or peripheral vascular disease.[2] Aric study followed 13,150 participants over 17.7 years and it showed that patients with Ankle Brachial Index (ABI) less than 0.90 (hazard ratio: 1.40; 95% confidence interval: 1.12 to 1.74) were at higher risk of developing heart failure.[3]

Framingham risk factors for cardiovascular disease includes age, gender, lipid panel components (cholesterol, low density lipid particle), elevated blood pressure as well as existence of blood pressure treatments. It does not take in account race differences. Although, its applicability should not be extended to heart failure the presence of these factors can help clinicians suspect coronary artery disease as a cause of heart failure.

DEFINITIONS, CAUSES AND PATHOPHYSIOLOGY

The Clinical syndrome of heart failure is characterized by impairment in the ventricular filling, diastolic dysfunction or inability of the heart eject blood or pump failure. Left ventricular dysfunction can occur independent of ejection fraction (EF). Newer classifications by American College of Cardiology Foundation and American Heart Association (ACCF/AHA) are based on ejection fraction and are defined as heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). However one can take in consideration other echocardiographic parameters when classifying heart failure.

HFrEF is defined by an EF less than 40%. Major causes of heart failure with preserved ejection fraction are coronary artery disease (CAD) with known myocardial infarction (MI), hypertension, diabetes mellitus, metabolic disease, atherosclerotic disease, and peripheral vascular disease (PVD). Borderline HFrEF is defined by an EF between 41% to 49% with attributes, treatments and outcomes similar to HFpEF.

HFpEF is a syndrome characterized by normal ejection fraction and left ventricular diastolic dysfunction observed on echocardiography or cardiac catheterization. The most important risk factor is hypertension.

Address correspondence to: Lucia Szabo, DO
Broward Health Medical Center, Fort Lauderdale, Florida
Email: luciaszabo.us@gmail.com

The ACCF/AHA stages of heart failure are classified as Stage A, B, C or D. This include patients at risk of heart disease, presence of structural heart disease and absence of symptoms, presence of structural heart disease and presence of symptoms and last refractory heart failure.

The New York Heart Association (NYHA) functional classification encompasses four classes based on exercise capacity and patient'symptoms. This classification represents an independent predictor of mortality and it is tailored to patients with structural heart disease mostly Stages B and C.

Other causes of heart failure are kidney failure, pericardial effusions, myocarditis, arrhythmias and valvular diseases. Endocrine disorders also have been implicated in pathophysiology of heart failure. For example, obesity impacts the workload of the heart secondary to increased circulatory blood volume. Likewise, diabetes mellitus is an independent factor for heart failure. The relationship between Hemoglobin A1c and mortality is "U" shaped with highest mortality at very low or very high Hemoglobin A1c. Patients with thyroid disease can have heart disease secondary to tachycardia and atrial fibrillation related the elevated levels of thyroid hormones. Patients can experience a hypothyroidism related decrease in myocardial contractility and decreased cardiac filling resulting in low cardiac output.

Dilated cardiomyopathy (DCM) refers to dilated ventricles and decreased contractility in absence of hypertension or valvular disease. Dilated cardiomyopathy is not a synonym for nonischemic cardiomyopathy, as the latter can be secondary to hypertension or valvular disease. Familial cardiomyopathies include those who have at least two closely related members with idiopathic cardiomyopathy. *(See Table 1 on page 12).*

HISTORY

A detailed history of present illness usually provides clues to diagnosis of heart failure. Family history may provide information suggestive of a familial cardiomyopathy defined as ≥ 2 relatives with idiopathic DCM. Duration of the symptoms may provide information on ability to recover over time when symptoms are more recent and adaptive processes have not been completed. Symptoms characterization, trigger factors for shortness of breath, presence of chest pain, dyspnea on exertion or exercise intolerance, can all be used in assessment of the NYHA class and clarify if coronary ischemia is the culprit. Symptoms of orthopnea or shortness of breath with recumbent position provide useful information suggestive of elevated left atrial pressures. It occurs secondary to redistribution of blood volume in the pulmonary splanchnic beds. This combination of decreased compliance and inability of left ventricle to pump will result in pulmonary congestion and subsequent symptoms. Orthopnea not improving with chest elevation may be a sign of mitral stenosis. Dyspnea for less than one minute in supine position with absence of symptoms after one minute may be suggestive of pulmonary arterial hypertension. Paroxysmal nocturnal dyspnea is shortness of breath occurring two to fours hours after falling asleep. Left ventricular heart failure is suggested by symptoms relieved with sitting or dangling the feet on the site of the bed. Presence of palpitations may suggest underlying atrial fibrillation or ventricular tachycardia. Decreased exercise tolerance may be difficult to differentiate from physical deconditioning or pulmonary disorders. Gastrointestinal symptoms such as weight loss may indicate cardiac cachexia, which itself carries a poor prognosis. Conversely, fluid overload is implied by weight gain, lower extremity edema, or ascites. Sleep problems may indicate fluid in the lungs, obstructive sleep apnea or pulmonary hypertension. Compliance to medications and diet such as sodium and fluid intake should be investigated.

PHYSICAL EXAM

The physical exam should begin with assessment of Body Mass Index (BMI), blood pressure, and orthostatic changes and continue with palpation of the pulse for strength and regularity. Changes in orthostatic blood pressure may indicate volume depletion or vasodilation. It is important to identify heart sounds such as S3 and signs of fluid overload such as jugular venous distention. S3 represents a low intensity sound heard in early diastole that most of the time is difficult to auscultate. Presence of S4 may indicate diastolic dysfunction or stiff ventricle. Pulmonary crackles, wheezing, decreased breath sounds or Cheynes-Stokes breath sounds consisting of apnea alternating with hyperapnea may occur. Pulmonary rales may not be present in patients with chronic heart failure due to increased lymphatic drainage. Cardiomegaly is suggested by a displaced point of maximal impulse. Hepatojugular reflex may occur and represents a sign of increased jugular venous pressure with palpation of abdomen. Cold lower extremities may indicate decreased cardiac output. Other symptoms include sinus tachycardia, pitting lower extremity edema, hepatomegaly, and possibly an alternating weak and strong pulse suggestive of left ventricular systolic dysfunction. Superimposed functional murmurs of mitral regurgitation or tricuspid regurgitation imply a diagnosis of dilated cardiomyopathy. *(See Table 2 on page 13).*

TABLE 1:
Causes of Cardiomyopathies

Etiology	Detailed Causes	Miscellaneous
Toxic	Cocaine Abuse	Can cause coronary vasospasm and left ventricular dysfunction
	Alcohol	Causes dilated ventricles when there is history of alcohol abuse for more than five years
Medication induced: chemotherapeutic agents	Anthracyclines, taxoids, interferons, and cyclophosphamide	Increase morbidity
Other Toxic Agents	Anabolic steroids, chloroquine, amphetamines, methylphenidate or catecholamines	Used to enchance performance or for weight loss. Ephedra may lead to left ventricular dysfunction and heart failure.
Rate Related	Tachycardia induced cardiomyopathy	Secondary to increased ventricular rate and premature ventricular complexes. Ventricular pacing or right ventricular pacing may result in exacerbation of heart failure.
Connective Tissue Disorder	Systemic lupus erythematosus (SLE), rheumatoid arthritis or scleroderma	Myocardial fibrosis, severe left ventricular dysfunction, conduction abnormalities
Infections	Human immunodeficiency virus (HIV) infections, Chagas disease	DCM Apical aneurysms, mural thrombi, change in configuration of ventricular walls
Noninfectious Causes	Hypersensitivity reactions to medications: Penicillin, Isoniazid, and Phenytoin	Can result in infiltration of myocardium with eosinophils or lymphocytes causing arrhythmias and sudden cardiac death
Peripartum Cardiomyopathies	Unknown Cause	Likely to occur in the third trimester and the risk increases with subsequent pregnancies. The risk of venous thromboembolism is high; and patients will require anticoagulation. Symptoms tend to persist four to six months postpartum, but some patients do not recover their ventricular function.
Other Infiltrative Diseases	Hemochromatosis, amyloidosis or sarcoidosis	May result in heart failure, left ventricular dysfunction, AV blocks, arrhythmia and sudden cardiac death most likely secondary to fibrosis
Stress Induced	Takotsubo cardiomyopathy	Occurs in absence of atherosclerosis. Associated with emotional or physical stress resulting in coronary vasospasm. Patients may experience elevated troponin level and apical ballooning.

TABLE 2:

Differential Diagnosis

Differential Diagnosis	Special Considerations
Pneumonia	Fever, productive cough, Focal signs of consolidation of chest xray, elevated WBC
Asthma	Wheezing on physical exam, can be a symptom of cardiac asthma, usually no other signs of heart failure like S3, JVD, edema
Pulmonary Embolism/DVT	Usually prolonged immobilization, recent surgery or trauma, hemoptysis, pleuritic chest pain, lower extremity edema EKG: sinus tachycardia, S1Q3T3, CT angiogram positive for thrombus
Interstitial Lung Disease	Progressive dyspnea, fine rales on auscultation, high resolution CT:reticular infiltrates, ground glass appearance, honeycombing, restrictive pattern on spirometry
Acute Respiratory Distress Syndrome	Hypoxia, bilateral infiltrates, insert pulmonary artery catheter if cannot differentiate from heart failure with usual diagnostic tests
Pericardial Disease	Chest pain better when leaning forward, Fever, shortness of breath, pericardial friction rub; EKG: electrical alternans, ST elevation with PR depression; pericardial effusion or fibrosis on echocardiogram
Nephrotic Syndrome	Decreased albumin, elevated triglicerides, protein on twenty four hours urine collection >3.5 g
Cirrhosis	Jaundice, hepatomegaly, edema, ascites, abnormal liver function tests, ultrasound liver will show ascites and cirrhotic changes

DIAGNOSIS

Congestive heart failure is a clinical diagnosis. Primary care physician should evaluate carefully history and physical exam and use diagnostic modalities to reinforce clinical diagnosis or to exclude other etiologies. Laboratory data can contribute to diagnosis and help clarify the cause of heart failure. Comprehensive blood count, comprehensive metabolic panel, liver function tests, thyroid function tests, urinalysis, and electrocardiogram should be performed. A decreased hemoglobin and hematocrit can point to high output failure possibility. Elevated blood urea nitrogen and creatinine may be a result of decreased cardiac output or intrinsic kidney injury. An increase in liver function tests may occur secondary to right sided heart failure or hepatic congestion. Thyroid function tests will diagnose hypothyroidism and hyperthyroidism; both diseases can be a primary cause or a contributing factor of heart failure. Urinalysis may show proteinuria suggestive of possible nephrotic syndrome as underlying cause for symptoms. When history, physical exam and laboratory data suggest alternative causes it is reasonable to perform diagnostic tests for hemochromatosis, amyloidosis and pheochromocytoma. If the patient presents with signs and symptoms of heart failure but the diagnosis is unclear, the clinician can verify the levels of Brain Natriuretic Peptide (BNP). An uncertain diagnosis may occur in a patient with superimposed symptoms of COPD. Other noncardiac conditions that can cause high BNP are sepsis, burns, renal failure, age and anemia. Lower levels of BNP have been reported with obesity. BNP levels can be used to guide therapy. However, the TIME-CHF trial failed to show change in quality of life or mortality between BNP guided therapy versus symptom guided treatment despite an augmentation in therapy in BNP group.[4] A BNP level of less than 100 in acute settings and a level of 35 with gradual onset of symptoms levels will exclude heart failure. Levels of troponins may

be elevated in patients with myocardial injury or necrosis, impaired hemodynamics, left ventricular dysfunction and presence of acute coronary syndrome. Congestion should be evaluated with chest radiograph with awareness that patients with chronic heart failure may not show any signs of pulmonary congestion secondary to compensatory effect of the lymphatic system. Echocardiogram will assess left ventricular function, size of atria and ventricles, wall motion abnormalities, wall thickness, valvular disease, inferior vena cava diameter and right ventricular pressure. Patients with high suspicion of coronary artery disease should undergo left heart cardiac catheterization. Hemodynamic assessment with right heart catheterization should be performed when there is unclear volume status, patient is refractory to treatment, has low blood pressures and worsening renal function.

TREATMENT

The primary care physician should be able to manage patients with heart failure. Clinicians should understand evidence based medicine and refer to clinical trials to administer treatments in accordance with population studied and based on common results. Hospitalization should be considered in patients with acute decompensated heart failure, pulmonary edema or cardiogenic shock requiring an acute intervention, intravenous inotropes, mechanical assist devices or hemodynamic monitoring. Referral to cardiology should be in case of suspected underlying coronary artery disease that necessitates interventions, refractory heart failure, or underlying rhythms that may require further testing or procedures. Medical treatment and nonpharmalogical interventions should be focused on close monitoring of symptoms and response or lack of response to therapy. Home environment should be accommodated to such extent that patient has eliminated all foods that might aggravate symptoms of heart failure. A scale should be made available for daily weights. Additional education on diet consisting of salt intake and fluid restriction should be addressed at every visit. Outpatient monitoring of compliance to medications by social services via telephone, mail or text message might be beneficial. Nurse home visits may be adequate to assess environment, perform tests and again monitor adherence to treatment.

Special consideration should be given to elderly patients, as they comprise a large population with heart failure with continual rise in incidence and prevalence of disease. Treatment should be tailored based on comorbidities by avoiding drastic decreases in blood pressure as these changes may increase the risk of falls. Elderly patients already have decreased glomerular filtration rate secondary to aging. Therefore, caution is advised when using diuretics or aldosterone receptor antagonists as they may either worsen renal function or cause cardiac abnormalities due to hyperkalemia. Treatment with digoxin may results in adverse effects in elderly secondary to low body mass index or renal dysfunction. Coadministration of medications such as verapamil, amiodarone, antibiotics (chlarithomycin or erythromycin), or antifungals (itraconazole) may increase digoxin level leading to digoxin toxicity.

STAGE A HEART FAILURE

Stage A heart failure includes patients at risk of heart failure, but without structural heart disease and involves elevated systolic and diastolic blood pressure. For this reason the focus should be placed on controlling hypertension. Medications should be administered to address comorbidities such as diabetes or atherosclerotic disease. In patients with diabetes, blood pressure should be managed with Angiotensin converting enzyme inhibitor (ACEI) or Angiotensin receptor blocker (ARB). A statin should be added to control hyperlipidemia in patients with coronary artery disease or at risk of developing myocardial infarction according to their Framingham score. Risk factors such as obesity, smoking, alcohol, cocaine and amphetamine use should also be addressed. Additionally, patients should be counseled at every visit about the risks associated with their habits.

STAGE B HEART FAILURE

Stage B heart failure includes patients with structural heart disease, but without signs and symptoms of heart failure. Patients with a family history of cardiomyopathy, long standing history of hypertension, prior myocardial infarction or receiving cardiotoxic agents should be evaluated with an echocardiogram. Studies such as COPERNICUS and CAPRICORN compared carvedilol to placebo and showed the benefit of beta blockers (BB) in heart failure. Capricorn trial showed a 23% relative reduction in mortality when medication is started 3-21 days after myocardial infarction (MI) in patients with reduced left ventricular function <40%.[5] The Copernicus trial showed a 35% relative risk reduction in mortality. In both trial patients were also receiving ACEI.[6]

Patients with low EF, but without symptoms of heart failure should receive treatment with ACEI or ARBs and BB. SAVE trial randomized 2231 patients to Captopril and placebo and showed a reduction in mortality in patients with MI and LVEF less than 40% without evidence of overt heart failure.[7] Val-HeFT trial randomized valsartan to placebo and showed no mortality benefit when added to ACEI or BB. There was statistical significant reduction in a morbidity associated with heart failure.[8] VALIANT study showed that Valsartan was non-inferior to Captopril in patients with heart failure, but failed to show a mortality benefit. If a patient has DM and

HTN consideration should be given to ACEI or ARBs. In a patient with refractory hypertension, spironolactone can be added to the regimen.[9] RALES trial included 1663 patients NYHA Class III-IV with EF less than 35% and randomized patients to 25 mg spironolactone daily and placebo. Trial demonstrated a 30% reduction in mortality, progressive reduction in heart failure, rate of hospitalization and sudden cardiac death.[10] EMPHASIS- HF trial randomized Eplerenone to placebo and included 2737 patients with NYHA class III-IV and left ventricular EF less than 30%. The study showed a 34% reduction in the risk of death from CV causes and hospitalization for HF.[11]

Newer trials such as PARADIGM-HF examined the effect of Neprilysin in patients with heart failure. Neprilysin is an endopeptidase that breaks down peptides such as BNP, bradykinin, and adrenomedullin contributing to decreased remodeling, vasoconstriction and sodium retention. "LCZ696" is the resulting product of combining angiotensin receptor neprilysin inhibitor (ARNI) such as neprilysin sacubitril with valsartan. Patients included in the trial displayed NYHA class II-IV symptoms, left ventricular ejection fraction less than 40% and were receiving beta blockers and ACEI. Patients were randomized to a single blind run-in period, during which all patients received enalapril for 2 weeks. Thereafter, medication was stopped for 1 day then all patients received ARNI for 4-6 weeks. Following run-in phase patients were randomized to ARNI and enalapril. Upon a 27 month follow up a reduction in mortality was noted in ARNI group as well as reduction in cardiovascular mortality and HF hospitalization. However, the risk of adverse effects were higher in ARNI group.[12]

STAGE C HEART FAILURE

Majority of the patients that present to emergency room are Stage C heart failure meaning they are symptomatic and have structural heart disease. This category of patients should monitor their weight, salt intake, exercise (if their functional status allows) and take medications as prescribed. A regimen consisting of ACEI or ARBs and BB. should be administered. Consideration should be given to volume status; while overload should be treated with diuretics. In patients of African American race, hydralazine and nitrates in combination are advised.

Aldosterone antagonists presents a choice if patients have NYHA Class II-IV symptoms and GFR greater than 30; or potassium levels less than 5.0. Diuretics should be added to standard regimen if there is evidence of fluid retention. Caution is advised when ACEI are prescribed and patients experience SBP less than 80, creatinine is greater than 3.0, potassium greater than 5.0 or there is bilateral renal stenosis. Contraindications to ACEI include angioedema and pregnancy. ARBs have demonstrated reduced hospitalization and mortality in heart failure and remain an alternative in patients intolerant to ACEI experiencing cough. Patients experiencing angioedema while on ACEI should not be started on ARBs as some patients can develop angioedema while on latter medication.

Beta blockers such as Carvedilol, Bisoprolol and Metoprolol have shown reduced mortality and hospitalization. The Seniors trial included patients with HFpEF that showed that Nebivolol can cause a small reduction in mortality in elderly patients.[14] Beta blockers can be used in patients with reactive airway disease or low heart rate if they are asymptomatic. Doses should be adjusted if patient becomes bradycardic with associated dizziness or second or third degree Atrioventricular (AV) block. Beta blockers should be discontinued when patient becomes hypotensive. Aldosterone receptors antagonists have been shown to reduce mortality in patients with HFrEF according to RALES trial, EPHESUS and EMPHASIS-HF trials.[10, 11, 13] Creatinine should be at a level of less than 2.0 in females and less than 2.5 in males, while potassium should be less than 5.0 at initiation of treatment. Potassium levels can be monitored within two to three days then at seven days.

Most available data shows that Hydralazine and isosorbide dinitrate have been effective in reducing mortality, but not the rate of hospitalizations. Combination regimen represents an alternative in patients unable to take ACEI or ARBs secondary to renal insufficiency, hypotension or allergic reaction. Hydralazine/isosorbide dinitrate should be used in the African American population and in conjunction with ACEI or ARB and aldosterone antagonists as it has shown in clinical trials to increase survival in patients with NYHA Class III-IV.[15] Treatment should start at 37.5 mg hydralazine and 20 mg tid isosorbide dinitrate titrate up to a maximum of 225 mg hydralazine and 120 mg of isosorbide dinitrate. V-HePT trial in 1984 randomized hydralazine/isosorbide to prazosin and placebo, but failed to show a survival benefit when compared the three groups.[8] A-HEFT trial showed a 40% reduction in mortality when combination drug was added to standard therapy consisting of ACEI, BB and diuretics.[15]

Digoxin reduces rate of hospitalization, but has no impact on mortality.[17] It should be considered in patients with heart failure with persistent symptoms despite use of ACEI and aldosterone antagonists. Practitioners should not institute treatment with digoxin in patients with AV block unless a pacemaker is present. Be cautious when a patient is on medications that can depress AV node, such as amiodarone or BB. However, studies have shown that digoxin works well in conjunction with BB to control ventricular response in patients with atrial fibrillation and heart failure. Digoxin toxicity occurs at levels greater than 2 ng/ml or at lower levels

of digoxin with low potassium or low magnesium as well as in patients with hypothyroidism, low lean body mass or renal dysfunction.

Administer anticoagulation in patients with HFrEF with atrial fibrillation having the following risk factors: hypertension, diabetes mellitus, prior stroke or TIA, and an age greater than 75 as calculated by CHADS2 score. Always consider that risk of thromboembolic stroke is 1-3% even in patients with low EF and intracardiac thrombi. The pathophysiology of increasing risk of cerebrovascular accident is related to the stasis of the blood in hypokinetic chambers and blood vessels leading to increased activity of procoagulant factors. Anticoagulation with warfarin or newer anticoagulants such as Rivaroxaban, Apixaban and Dabigatran should be initiated when patients with heart failure and atrial fibrillation, and at least one risk factor identified by CHADS2 score. The newer anticoagulants do not require INR monitoring which may be overwhelming to patients. The data is insufficient regarding use of aspirin in patients with heart failure, but no evidence of atherosclerotic disease manifested as prior myocardial infarction or coronary artery disease.

Statins should not be used in patients with heart failure without evidence of atherosclerotic disease. The Corona trial observed the role of Rosuvastatin in patients with ischemic heart failure, NYHA class II-IV, and failed to show a difference between placebo and rosuvastatin in primary end points such as cardiovascular mortality, non-fatal MI and nonfatal stroke. There was a reduction in hospitalization secondary to cardiovascular causes in patients on rosuvastatin.[18] The Gissi-HF study observed patients with ischemic and nonischemic HF while taking Rosuvastatin and failed to show a change in clinical outcomes.[19]

Omega-3 polyunsaturated fatty acids (PUFA) have not reach statistical significance in reduction of all cause mortality in HISSI-HF trial.[20] A total of 6975 patients with NYHA class II-IV patients were randomized to 1 gm of PUFA and placebo. There was a borderline statistically significant reduction in time to death or admission to hospital for heart failure. Nutritional supplements are not recommended for treatment of heart failure except to replenish deficiencies.

Antiarrhythmics such as Class I and class III sotalol and dronedarone should be avoided in patients with heart failure. Amiodarone and dofetilide can be used because of a neutral effect on mortality. Calcium channel blockers have negative inotropic effect and can slow conduction in calcium dependent sinoatrial (SA) node and AV node. Both should be avoided in heart failure. The Praise trial demonstrated that amlodipine causes no harm in patients with HF NYHA class III-IV with ejection fraction less than 30%.[21]

NSAIDS inhibit synthesis of prostaglandins resulting in vasoconstriction, reabsorption of salt in loop of Henle and collecting tubule and water retention exacerbating the symptoms of heart failure.

AUTOMATIC IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (AICD)

The primary care physician should be aware of risk of sudden cardiac death in patients with heart failure and appropriately refer patients to electrophysiologist for further therapy specially when practicing in a rural area with decreased referral ability. The population who benefits from AICD placement includes patients at risk of recurrence of symptoms with associated ventricular tachycardia, ventricular fibrillation, history of sudden cardiac death and unexplained syncope. There is no net benefit in using ICD in patients within 40 days after acute MI. Madit-I and Madit-II showed a mortality benefit in patients with LVEF less than 35% at 40 days post-MI and NYHA Class II and III or patients with LVEF less than 30% at 40 days post-MI and NYHA Class I.[22, 23] Definite trial compared ICD and standard therapy and demonstrated a reduction in mortality in patients with nonischemic cardiomyopathy and LVEF less than 35 %, but it did not reach statistical significance. This trial showed a reduction in sudden cardiac death from arrhythmias that reached statistical significance.[24]

Patients with HFrEF should undergo goal directed medical therapy for three to six months followed by an echocardiogram to assess LV function. Although ICD seems to be a great device in reducing the risk of sudden cardiac death from ventricular arrhythmias, patients might have a decreased quality of life secondary to frequent shocks that may lead to a post-traumatic stress syndrome. It would be reasonable to administer antiarrhythmics and perform a catheter ablation in that situation, which may decrease the need for ICD shocks.

CARDIAC RESYNCHRONIZATION THERAPY (CRT) FOR VENTRICULAR PACING

The benefit of biventricular pacing is seen in improvement of pathophysiology in patients with heart failure and manifests as decreased remodeling of the heart, improved contractility of the ventricle, diminished secondary mitral regurgitation and improved EF. Indications for CRT pacing include mostly patients with HF NYHA class III and IV, wide QRS and left bundle branch block (LBBB). BLOCK HF trial randomized patients to right ventricular pacing and biventricular pacing. In patients with reduced EF biventricular pacing increased left ventricular end systolic volume index and decreased death and urgent care visit for heart failure.[25]

In patients with characteristics such as NYHA class I-II heart failure symptoms, EF less than 30 % and QRS greater than 130 ms, trials have showed better outcomes when treated with CRT-D alone when compared to ICD alone.[26] RAFT trial included patients with HF NYHA Class II-III and showed reduction in mortality with CRT. The role of CRT in HF NYHA Class I is unclear based on studies that have showed a reduction in hospitalizations with no difference in mortality.[27]

STAGE D HEART FAILURE (REFRACTORY)

Signs and symptoms of Stage D heart failure include cardiac cachexia, worsening renal function, low blood pressures, intolerance to ACEI or BB due to hypotension and persistent dyspnea. Other signs include increased use of diuretics to greater than 160 mg per day, addition of metolazone therapy and increased ED visits to greater than two per year for heart failure. Other causes for weight loss or dyspnea should be investigated. Workup should be sought for thyroid and pulmonary disorders as causes of worsening of the symptoms. Patients should be evaluated for medication compliance as another cause of treatment failure. Patients with stage D heart failure should undergo fluid restriction of 1.5-2 L daily. Fluid restriction with salt restriction may provide a better efficacy of diuretics. Limiting salt will result in better excretion of the water and less activation of vasopressin, which physiologically mediates water reabsorption in distal tubule. Patients experiencing cardiogenic shock should receive inotropic support, although inotropes have not demonstrated improved outcomes. Milrinone causes inhibition of phosphodiesterase 3 resulting in improved diastolic relaxation and vasodilation of arteries. Dobutamine and dopamine is involved in stimulation of adrenergic and dopaminergic receptors respectively. Patients with hypotension and decreased systemic perfusion, low cardiac index and systolic dysfunction will need inotropic support. In patients refractory to inotropic support, mechanical circulatory support can be used as a bridge to transplant or to candidacy for transplant if patients meets criteria for heart transplantation. Mechanical support devices are available in a variety of forms such as percutaneous or surgical. Such devices can assist the right, left or both ventricles, can provide continuous or pulsatile flow and can be used for short and long term management. These devices have shown an improvement in survival and functional capacity. Mechanical support devices are used as therapy in patients with pulmonary hypertension and heart failure who are not candidates for transplant due to irreversible elevated pulmonary arterial pressures. With the help of such devices, patients may become eligible for transplant over time. The REMATCH trial randomized 129 patients in end stage heart failure who were not eligible for transplant due to optimal therapy. The trial showed an improved mortality in patients with left ventricular assist device with an absolute risk reduction of 28.5%. The median survival of patients with Heartmate device was 408 days compared to 150 days in patients receiving standard therapy for heart failure. Patients included in the trial received inotropic support.[28]

Cardiac transplantation is considered the main treatment of the Stage D heart failure. Indications for heart transplantation includes patients with hypertrophic cardiomyopathy, reversible pulmonary HTN, peripartum cardiomyopathy and restrictive cardiomyopathy. Statistical analysis have shown better outcomes in these groups of patients.

ACUTE DECOMPENSATED HEART FAILURE

Hospitalized patients with heart failure can experience an acute coronary syndrome, accelerated hypertension, an acute decompensated heart failure, cardiogenic shock or acute right heart failure. A physician should assess the hemodynamics by looking at blood pressure, central venous pressure, degree of congestion (both wet and dry), and degree of perfusion hot or cold. Chest radiography should help diagnosis, but a negative chest X-ray does not exclude heart failure. BNP levels should guide treatment when diagnosis is uncertain. Levels should be adjusted for age, while low levels should not defer diagnosis when clinical picture is strongly suggestive of heart failure. Practitioners will identify causes that promoted the acute decompensation such as an acute coronary syndrome guided by electrocardiographic changes or troponin levels. Factors that may contribute to acute decompensation of heart failure include the following: medication noncompliance, ischemia, elevated blood pressure (especially in African American males and patients with HFpEF), atrial fibrillation, medications with negative inotropic support or medications that increase salt retention such as steroids, pulmonary embolus, alcohol, cocaine or methamphetamines, DM, and infections or valvular disease endocarditis.

On admission, oral medications will be continued and up titrated in absence of hemodynamic instability. ACEI and beta blockers should be reduced or withheld if patients manifest worsening renal failure or hypotension, marked volume overload or low cardiac output. Diuretics in patients with heart failure have shown to decrease morbidity. Patients with heart failure should be treated with diuretics to relieve congestion and in fashion to not cause a rapid decrease in intravascular volume. Electrolytes and daily weights, strict fluid intake and outtake should be monitored closely. DOSE trial evaluated the effects of administration of continuous infusion versus intermittent boluses with low dose and high dose diuretics in patients with heart failure. The high dose diuretic consisted of 130 mg IV bid. Notably, the Dose trial revealed that patients included in the study were already receiving a dose of 80 to

240 mg daily of furosemide for at least one month prior to hospitalization. The study did not show any improvement between study groups regarding global relief of symptoms or change in creatinine level. As secondary end point, high dose diuretics were associated with greater relief of dyspnea, change in weight, or net fluid loss at 12 hours. These differences were not seen with either intermittent boluses or continuous infusion of diuretics.[29] Currently, there are no studies showing the effect on mortality. If patients remain refractory to diuretics use after addition of a second diuretic, they should undergo assessment of filling pressures and cardiac output with right heart catheterization. A treatment option would be adding a low dose dopamine infusion to loop diuretics after all options have been exhausted. If these treatments are unsuccessful, patients should undergo treatment with ultrafiltration. UNLOAD and CARRESS-HF trials used different approaches to ultrafiltration. Both studies included critically ill patients refractory to treatment. CARESS-HF showed a change in creatinine level at 96 hours, but failed to show a change in clinical well being of the patient or reduction in dyspnea.[30] UNLOAD trial randomized 200 patients to ultrafiltration and IV diuretics showed an improvement in weight at 48 hours but failed to show an improvement in dyspnea score or length of hospitalization.[31] Patients with acute decompensated heart failure should receive nitroglycerin, nitroprusside or nesiritide in absence of hypotension. Nitroglycerin will decrease the venous preload and reduce pulmonary congestion. Patients with HF and hypertension, coronary ischemia and mitral regurgitation should be considered for administration of nitroglycerin. Sodium nitroprusside effects preload, afterload and relaxes pulmonary vasculature, but has the potential to cause hypotension. Thus, it is an excellent choice for patients with vascular congestion and significant mitral regurgitation affecting the left ventricular function.

ANTICOAGULATION

Patients with heart failure should receive prophylaxis for deep vein thrombosis, as decreased cardiac output, and venous stasis can promote clot forming. Treatment consists or Enoxaparin (Lovenox) 40 mg subcutaneous daily or Heparin 5000 units subcutaneously every eight hours. Graded compression stocking should be used with caution in patients with heart failure as they may contribute to cutaneous complications.

CARE AFTER HOSPITALIZATION

Upon discharge, patients should be enrolled in multidisciplinary heart failure disease management programs, and a follow up appointment should be scheduled within 7-14 days to reduce the risk of hospital readmission. Additionally, a telephone follow up within three days from discharge should address adherence to medications and change in behaviors. Cardiac rehabilitation has been shown to improve mortality, rate of hospitalization and functional capacity. Patient should be referred for supervised exercise training following discharge.

COMORBIDITIES

Comorbidities such as Atrial Fibrillation and Heart Failure as well as surgical considerations in heart failure

ATRIAL FIBRILLATION AND HF

Atrial fibrillation predisposes heart failure. However, heart failure is an independent risk factor for atrial fibrillation. Assessment should begin with history and physical examination to assess duration and type of atrial fibrillation. CHADS2-Vasc score represents an assessment tool used by physicians to determine need for anticoagulation in patients with atrial fibrillation. Components of CHADS-Vasc score include: congestive heart failure, HTN, age greater than 65, DM, stroke, vascular disease, age greater than 75 and sex. A score of 1 is assigned to all components except stroke or age greater than 75, which receives a score of 2. Score 0 does not require anticoagulation. Score 1 aspirin or other forms of anticoagulation can be considered based on a mutual decision between physician and patient. Score of 2 or greater requires anticoagulation as risk of stroke increases considerably. Patients should have an EKG to assess rhythm, left ventricular hypertrophy, bundle blocks, prior MI and atrial arrhythmias. Furthermore, an echocardiogram is warranted to assess for valvulopathy, right and left atrial size, right ventricular systolic pressure, atrial thrombus, left ventricular hypertrophy and pericardial disease. Laboratory data is necessary to assess thyroid and liver function tests, as well as electrolytes, BUN and creatinine. A transesophageal echocardiogram, electrophysiologic study or chest x-ray may be needed based on clinical presentation and results of above mentioned tests.

Patients who develop heart failure secondary to atrial fibrillation should undergo a rhythm control approach to improve their atrial preload. A newly diagnosed heart failure in presence of atrial fibrillation with rapid ventricular response can be addressed with a rate control therapy and assess response to therapy by monitoring ejection fraction. A second approach can be focused on rhythm control therapy consisting of amiodarone and cardioversion after one month. Patients with heart failure who develop atrial fibrillation can receive treatment with a rate control agent or an antiarrhythmic since both approaches seem to be non-inferior. Improvement with antiarrhythmics is observed when patients underwent catheter ablation. Practitioners should remember that beta blockers have a mortality reduction benefit. Digoxin can be added to treatment with beta blockers or calcium channel blockers. Procedures such as catheter ablation and CRT placement should be considered when atrial fibrillation is refractory to treatment with antiarrhythmics.

Patients with heart failure with preserved ejection fraction and atrial fibrillation typically experience shortened diastolic filling time and loss of atrial kick to left ventricular diastolic filling. These patients can be treated with ACEI or ARBs and beta blockers.

SURGERY AND HEART FAILURE

Patients with heart failure should undergo revascularization in the presence of 50% stenosis of the left main or 70% stenosis of coronary arteries and EF 35-50%. Surgical intervention may include mitral or aortic valve replacement, septal myectomy for hypertrophic cardiomyopathy or ablation for ventricular arrhythmias. STICH-1 trial included 1212 patients with LVEF less than 35% randomized to CABG versus optimal medical therapy showed no mortality benefit from any cause but there was a decrease in mortality and hospitalization from cardiovascular events. This trial excluded patients with left main stenosis greater than 50%.[32] STICH-2 trial failed to show a mortality benefit in patients who underwent surgical ventricular reconstruction in addition CABG to CABG alone.[33]

Heart failure with preserved ejection fraction has not been addressed much by current clinical trials. Little is know about effectiveness of standard medications in this population. The TOPCAT trial randomized 3,445 patients to spironolactone and placebo. Patients included had LVEF greater than 45%, findings of heart failure or elevated levels of BNP. There was no difference in primary outcome regarding CV mortality. A decrease in hospitalizations in patients in North America was noted, but the finding was not consistent in sample population from Eastern Europe. Geographic disparities might be secondary to overdiagnosis of heart failure or variability in heart failure practices.[34]

Although heart failure diagnosis and treatment approach may be a challenging task to the practitioner, the goal of treatment of heart failure is to control BP, reduce symptoms and risk factors in order to prevent morbidity. This goal can be achieved by providing a medication regimen individualized to a particular patient.

TABLE 3:

Summary of Treatment

Stages of Heart Failure	Treatment	Goals
Stage A	ACEI, ARBs, Statins	Treat HTN, DM, obesity
Stage B	ACEI, ARBs, BB, Statins ICD if apppropriate	Prevent further cardiac remodeling
Stage C	Diuretics, BB, ACEI or ARBS, Aldostorone antagonists, Hydralazine/Isosorbide dinitrite if African American race, Digoxin, ICD or CRT if appropriate	Address HTN, DM, obesity Symptoms control, prevention of hospitalization; decrease mortality
Stage D	Heart transplant, Ventricular assist device, Palliative care, Hospice, Inotropes, ICD deactivation	Symptoms control, Decrease rate of hospitalizations, End of life care
Acute Decompensated Heart Failure	Diuresis, If unsuccessful add second agent, or consider ultrafiltration; Inotropes: Dopamine, Dobutamine, Milrinone; Nitroglycerin if HF and HT, coronary ischemia or mitral regurgitation; Continue ACEI and BB if tolerated or reintroduce as soon as patients tolerates, DVT prophylaxis; If hyponatremia consider Tolvaptan; Noninvasive ventilation: CPAP or BIPAP	Find cause or precipitant; Dopamine low dose as adjunct to diuresis to improve renal function; Pulmonary artery catheter does not improve survival; Milrinone: causes peripheral and pulmonary vasodilation, do not administer unless patient is in shock; Dobutamine use in cardiogenic shock, increases heart rate and oxygen demand

REFERENCE

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013 Oct 15;128(16):e240-327.
2. Ather et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol. 2012 Mar 13;59(11):998-1005. doi: 10.1016/j.jacc.2011.11.040
3. Guota et al. Heart Failure Risk Across the Spectrum of Ankle-Brachial Index: The ARIC Study (Atherosclerosis Risk In Communities). JACC Heart Fail. 2014 Oct;2(5):447-54. doi: 10.1016/j.jchf.2014.05.008. Epub 2014 Sep 3.
4. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, Vuillomenet A, Jeker U, Dubach P, Beer H, Yoon SI, Suter T, Osterhues HH, Schieber MM, Hilti P, Schindler R, Brunner-La Rocca HP; TIME-CHF Investigators. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA. 2009 Jan 28;301(4):383-92.
5. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001 May 5;357(9266):1385-90
6. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002 Oct 22;106(17):2194-9.
7. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992 Sep 3;327(10):669-77
8. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001 Dec 6;345(23):1667-75.
9. McMurray J, Solomon S, Pieper K, Reed S, Rouleau J, Velazquez E, White H, Howlett J, Swedberg K, Maggioni A, Køber L, Van de Werf F, Califf R, Pfeffer M. The effect of valsartan, captopril, or both on atherosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). J Am Coll Cardiol. 2006 Feb 21;47(4):726-33.
10. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999 Sep 2;341(10):709-17.
11. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011 Jan 6;364(1):11-21.
12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004.
13. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003 Apr 3;348(14):1309-21.
14. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Böhm M, Anker SD, Thompson SG, Poole-Wilson PA; SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005 Feb;26(3):215-25.
15. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN; African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure.N Engl J Med. 2004 Nov 11;351(20):2049-57.
16. Loeb HS, Johnson G, Henrick A, Smith R, Wilson J, Cremo R, Cohn JN. Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. The V-HeFT VA Cooperative Studies Group.Circulation. 1993 Jun;87(6 Suppl):VI78-87.
17. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997 Feb 20;336(8):525-33.
18. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, 1McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J; CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007 Nov 29;357(22):2248-61
19. Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Oct 4;372(9645):1231-9.
20. Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Oct 4;372(9645):1223-30.
21. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, Cropp AB, DeMets DL. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. N Engl J Med. 1996 Oct 10;335(15):1107-14.
22. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002 Mar 21;346(12):877-83.
23. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996 Dec 26;335(26):1933-40.
24. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaechter A, Levine JH; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators.Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004 May 20;350(21):2151-8.

25. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, Sutton MS; Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med. 2013 Apr 25;368(17):1585-93.

26. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009 Oct 1;361(14):1329-38.

27. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010 Dec 16;363(25):2385-95.

28. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001 Nov 15;345(20):1435-43.

29. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011 Mar 3;364(9):797-805.

30. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012 Dec 13;367(24):2296-304.

31. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA; UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007 Feb 13;49(6):675-83. Epub 2007 Jan 26. Erratum in: J Am Coll Cardiol. 2007 Mar 13;49(10):1136.

32. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL; STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med. 2011 Apr 28;364(17):1607-16.

33. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, Hill JA, Menicanti L, Sadowski Z, Desvigne-Nickens P, Rouleau JL, Lee KL; STICH Hypothesis 2 Investigators. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med. 2009 Apr 23;360(17):1705-17.

34. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014 Apr 10;370(15):1383-92.