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Heart Failure
An Epidemic of the 21st Century

Lana Tsao, MD, and C. Michael Gibson, MD

Abstract: Heart failure is the leading cause of hospital admissions in the United States and one of the leading causes of morbidity, mortality, and resource utilization in this country. This diagnosis carries an ominous prognosis worse than most cancer, and the financial burden exceeds 25 billion dollars a year. With the aid of a plethora of drugs, devices, and complementary therapies, heart failure management and outcomes have improved. However, as the country ages and more people survive their myocardial infarctions, as well as develop hypertension and diabetes, the incidence of heart failure continues to escalate. Heart failure has become such a broad epidemic that the American College of Cardiology, in collaboration with the American Heart Association, has developed new guidelines to prevent the development of systolic heart failure, thus changing the emphasis from clinical assessment to detection, intervention, and prevention. Hypertension and diabetes mellitus, in particular, are targeted as major risk factors for heart failure. These guidelines consist of 4 stages and provide objective categorization and evidence-based treatment recommendations from the literature for each of the stages.

Inroads were made in the fight against heart attacks by the formation of care teams. Similarly, care teams for early identification of patients at risk, development of algorithms and critical pathways, and practicing evidence-based medicine are all within our capabilities for the battle against heart failure. Toward this end, the National Coalition for the Management of Left Ventricular Dysfunction has been formed and invites you to join in this comprehensive project to impact on the course of the heart failure epidemic at www.nclvd.org.

Key Words: heart failure management, heart failure treatment algorithms

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Heart failure, which can be due to systolic or diastolic dysfunction, is an endemic and escalating health care problem. A constellation of signs and symptoms, heart failure is a syndrome characterized by pulmonary and systemic venous congestion due to cardiac dysfunction. This disease is largely a disease of the elderly, and its incidence continues to grow as the population ages and as more patients survive following myocardial infarction (MI). The incidence of heart failure is approximately 1% for adults between the ages of 50 and 59 years old. This, in turn, doubles every decade, to almost 10% for men and women between the ages of 80 and 90 years old.[1] At present, internists and family physicians manage the majority of patients with heart failure.

Data from clinical trials in systolic heart failure has revolutionized the management of these patients. Heart failure has become a more readily manageable disease, and patients can now expect to have an improved quality of life and long-term survival. Unlike coronary artery disease and stroke, for which incidence and mortality continue to decline, heart failure is increasing in frequency, and because of the rise in incidence of the disease, the absolute number of deaths remains high. This is despite an armamentarium of pharmacologic agents and complementary therapies such as cardiac resynchronization, ventricular assist device support, and cardiac transplantation. More deaths result from the combination of heart failure and sudden cardiac death (SCD) than all forms of cancer combined.[1] The 5-year mortality after diagnosis of HF has been estimated at approximately 50%.[2] Even patients with asymptomatic left ventricular dysfunction have a decreased life expectancy. Annual expenditures from this disease exceed $30 billion. The emotional burden is incalculable.

AQ: 1

Etiology and Risk Factors for Heart Failure

There are multiple causes of heart failure. In men, systolic dysfunction is more frequent, while in women diastolic dysfunction is the predominant etiology of heart failure.[3] The leading risk factor for systolic dysfunction in this country is coronary artery disease. As more and more patients are surviving myocardial infarcts, the expectation is that the incidence of heart failure will rise. The common link between

the development of coronary artery disease and cardiomyopathy is hypertension.[4]

The evolution of heart failure is such that hypertension predisposes to both MI and cardiomyopathy.[5,6] The lifetime risk for developing heart failure in patients without coronary artery disease is 1 in 9 for men and 1 in 6 for women due to hypertension,[4] indicating the impact of this disease, especially in the elderly.[7] In addition, those patients who have the metabolic syndrome, which consists of diabetes, hypertension, hyperlipidemia, and obesity, are at risk for the development of heart failure. Diabetes mellitus is a powerful and independent risk factor for cardiovascular morbidity and mortality, which accounts for almost 80% of the deaths in this disease. Not only is diabetes mellitus associated with an increased risk for ischemic heart disease and subsequent development of heart failure, but diabetes mellitus in conjunction with hypertension can lead to heart failure. Other independent risk factors for heart failure include obesity,[8] smoking,[9] valvular heart disease, renal insufficiency,[10] sedentary lifestyle, left bundle branch block, and family history of cardiomyopathy.

Classification

Heart failure has become such a broad epidemic that the American College of Cardiology, in collaboration with the American Heart Association, has developed new guidelines to emphasize prevention of systolic heart failure and its risk factors, thus changing the emphasis from clinical assessment to detection, intervention, and prevention. Although a large percentage of patients with heart failure have preserved LV function, thus far, clinical trials have focused on patients with systolic dysfunction. At the present time, these patients are risk stratified and managed according to clinical assessment and New York Heart Association functional class.

The New York Heart Association scheme includes classes I through IV. Class I patients are asymptomatic patients with known LV dysfunction. Class II patients are mildly limited but can perform all their own activities of daily living. NYHA class III HF patients have symptoms with minimal activity. Class IV patients are essentially moribund with symptoms at rest.

The new ACC/AHA classification focuses on patients with left ventricular systolic dysfunction and is meant to provide objective categorization and evidence-based treatment recommendations from the literature (Table 1).[11] This classification schema has 4 stages, with a recommended treatment plan for each stage, emphasizing disease prevention and the importance of altering the progression of heart failure. Underlying the treatment of all patients with heart failure is nonpharmacologic management. These measures stress the importance of general health, including restriction of fluid and salt intake, treatment of hypertension and lipid disorders, diabetes control, smoking cessation, and moderation in the use of alcohol.

Stage A identifies the at-risk population of patients who have not yet developed left ventricular dysfunction. These patients have a risk factor for heart failure, such as hypertension or coronary heart disease. However, structural heart disease has not yet developed. Of note in this classification system, diabetes mellitus is also recognized as a major risk factor for the development of LV dysfunction and ensuing heart failure. Treatment recommendations for this stage focus on lifestyle changes, encouraging diet and exercise. Lipid disorders, hypertension, and diabetes mellitus should all be aggressively treated. JNC VII outlines current recommendations for the management of hypertension.[12] All patients with diabetes mellitus should be on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

Stage B characterizes patients with structural heart disease but asymptomatic left ventricular dysfunction. Unless the patient's left ventricular dysfunction is identified in the postMI setting, these patients may be hard to identify as they

TABLE 1. Stages of Heart Failure and Recommended Treatment Options

Heart Failure Stage	Treatment Option
Stage A High risk with no symptoms	ACE inhibitors or ARBs in some patients
Stage B Structural heart disease; no symptoms (NYHA class I symptoms)	ACE inhibitors and ARBs in all patients β-Blockers in selected patients
Stage C Structural disease; previous or current symptoms (NYHA class II or III symptoms)	ACE inhibitors and β-blockers in all patients Diuretics and digoxin Aldosterone antagonist; nesiritide
Stage D Refractory symptoms requiring special intervention (NYHA class IV symptoms)	Inotropes Cardiac transplantation Mechanical circulatory assist

Adapted from Jessup M, Brozena S. Heart failure. *N Engl J Med*. 2003;348:2007–2018.

do not have symptoms. These patients do not have overt heart failure, similar to New York Heart Association class I patients. Patients in this stage continue with the same treatment measures as in stage A. However, ACE inhibitors or β-blockers are added to the regimen (Table 2).

Stage C includes patients with structural heart disease and known heart failure. Symptoms of heart failure such as fatigue, dyspnea on exertion, or reduction in activity have occurred. At this point, along with continuing the treatment recommendations from Stage A, patients are on all the standard heart failure medications, including ACE inhibitors, β-blockers, aldosterone antagonists, diuretics, and digitalis.

Stage D patients are analogous to New York Heart Association class IV patients, who, despite appropriate medical management, have refractory heart failure with persistent signs and symptoms of pulmonary venous congestion or low output state. At this point, advanced therapies such as ventricular assist devices, cardiac transplantation, or continuous inotrope infusion are considered. Alternatively, depending on the goals of therapy, patients may refuse further treatment and opt for hospice care.

TABLE 2. Body of Evidence for β-Blockers

Trial	Conclusions
US Carvedilol Study*	Carvedilol vs SD in 1094 patients over 7 mAnnualized mortality reduced by 42% (6.4% vs. 11.1%)*
CIBIS II†	Bisoprolol vs SD in 2647 patients over 16 mAnnualized mortality reduced by 33% (8.8% vs. 13.2%)
MERIT-HF‡	Metoprolol vs SD in 3991 over 12 m Annualized mortality reduced by 30% (7.2% vs. 11%)
BEST§	Bucindolol vs SD in 2523 patients over 24 mAnnualized mortality nonsignificantly reduced by 10% (15% vs. 17%)
COPERNICUS‖	Carvedilol vs SD in 2289 failing patients over 24 mAnnualized mortality reduced by 38% (11.4% vs. 18.5%)
CARMEN	Carvedilol improves LV remodeling

SD, standard deviation; LV, left ventricle.

*Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure: US Carvedilol Heart Failure Study Group. *Circulation.* 1996;94:2800–2806.

†The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353:9–13.

‡Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA*. 2000;283:1295–1302.

§Domanski M, Krause-Steinrauf H, Deedwania P, et al. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. *J Am Coll Cardiol*. 2003;42:914–922.

‖Packer M, Fowler MB, Roecker EB, 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;106:2194–2199.

Pathophysiology of Heart Failure

The natural history of heart failure is such that after the initial insult, patients fall into 2 separate categories. They can either decline rapidly or develop heart failure over a period of many months to years. The development of heart failure is at least in part due to neurohormonal activation of the renin angiotensin system and the sympathetic nervous system (Fig. 1), both of which contribute to the remodeling and progressive worsening of LV function.[13] This reduction in function occurs as a result of fibrosis, apoptosis, left ventricular hypertrophy, direct myotoxicity, and peripheral vasoconstriction with hemodynamic alterations. Initially, patients develop heart failure symptoms such as fatigue, decreased activity, pulmonary and vascular congestion, and peripheral edema with progressive dyspnea (Fig. 2). Eventually, this process amplifies morbidity and mortality due to arrhythmias and pump failure. Treatment strategies have focused on blocking neurohormonal activation and preventing LV remodeling using ACE inhibitors and β-blockers.

Identifying Patients With Heart Failure

Heart failure is the symptomatic and physical manifestation of systolic or diastolic cardiac dysfunction. Symptoms of heart failure can be due to a low cardiac output, volume overload, or elevated diastolic pressures. Symptomatic manifestations of low cardiac output can be nonspecific, such as fatigue or confusion, whereas patients with fluid overload present more typically with dyspnea on exertion or rest, suggesting pulmonary venous congestion, as well as orthopnea, paroxysmal nocturnal dyspnea, and ankle edema. On physical examination, the patients have jugular venous distention, which may be difficult to assess. Other findings can include a laterally displaced point of maximal impulse, a third heart sound, mitral regurgitation, and crackles on pulmonary auscultation. To differentiate the etiology of heart failure due

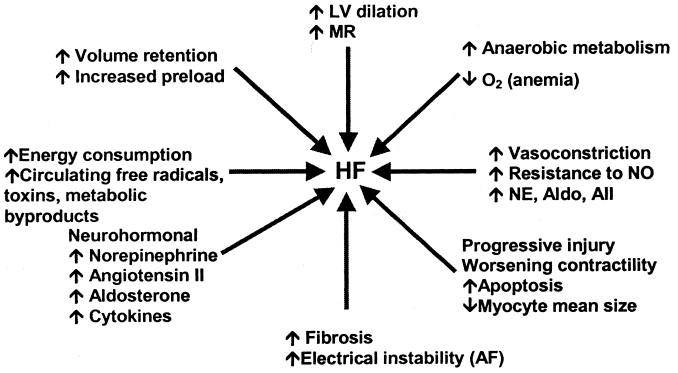

FIGURE 1. Factors leading to the development of clinical heart failure.

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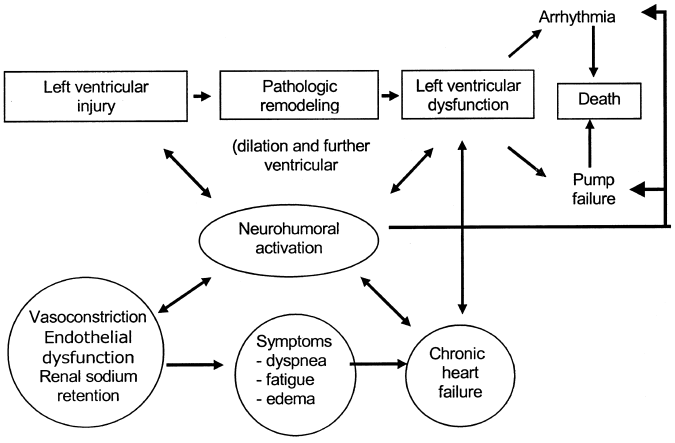

FIGURE 2. Risk factors.

to systolic dysfunction or preserved ejection fraction, echocardiography or radionuclide ventriculography is performed. Brain natriuretic peptide has recently been identified as a marker for heart failure and can also be useful in establishing the diagnosis.[14,15]

Strategies for the Prevention of Heart Failure

With the advent of the new ACC/AHA classification and guidelines, therapeutic interventions are now being recommended to control the hemodynamic consequences of hypertension and diabetes. These diseases have been earmarked as modifiable risk factors for the eventual development of LV dysfunction and probable heart failure. Consequently, part of the strategy to prevent heart failure is to intervene early to control risk factors for coronary artery disease. Thus, management of hypertension, treatment of lipid disorders, utilization of reperfusion strategies for acute MI, and the use of ACE inhibitors in asymptomatic LV dysfunction are all critical to preventing the development of heart failure.

While treatment of heart failure has been standardized in many ways, the aims of treatment are still individualized to each patient's needs. Overall, the goals of heart failure management are to prolong life, reduce symptoms, enable the patient to return to a more active lifestyle, decrease the incidence of hospitalization, and prevent the progression of the disease. Improving cardiac output, managing dysrhythmias, and preventing thromboembolic complications will help patients to achieve these goals.

Nonpharmacologic measures used to treat heart failure are a critical component of successful disease management. As previously described, one must first attempt to decrease the risk of recurrent cardiovascular injury with the control of hypertension, hyperlipidemia, and diabetes. Cessation of smoking must also occur for treatment to be truly successful. For the obese patient, weight reduction is critical. The importance of maintaining fluid balance by restricting salt intake to less than 2 g per day and by daily weight monitoring cannot be overemphasized. Poor nutritional intake and the development of cardiac cachexia in patients with severe heart failure contribute to the overall deconditioning of a patient, and it is important that patients have adequate nutritional intake. In addition, it is well documented that participation in an exercise program can improve the overall well-being of a patient, as well as their functional status and sense of self-sufficiency, which is essential to disease management. The patient with chronic heart failure is at risk for infection, which can precipitate worsening heart failure. Therefore, vaccinations against infections caused by pneumococcus, influenza, and hepatitis bacteria are also recommended.

Pharmacologic Treatment of Heart Failure

A plethora of drugs has been identified which improves and controls heart failure. Medications, which modify the progression of heart failure, include ACE inhibitors, β-blockers, ARBs, aldosterone antagonists, and hydralazine in combination with nitrates. Diuretics and digitalis treat symptomatic heart failure. The drugs that modify disease progression have been shown to decrease morbidity and mortality. On the other hand, drugs for the treatment of symptomatic heart failure may have less effect on disease progression but are nonetheless critical to the improvement of the patient's overall sense of well-being, as well as for symptomatic relief. More recently device therapy with internal cardiac defibrillators (ICD) and cardiac resynchronization (CRT) has been added to this regimen.

If optimal heart failure management does not control symptoms or prevent disease progression, cardiac transplantation is a potential option. If the patient's condition precludes transplantation, implantation of a left ventricular assist device as a bridge to an eventual transplant (and more recently as destination therapy) may be recommended. However, these heroic and often last-ditch measures may sometimes prolong patient suffering. Difficult as it may be and rather than delaying the inevitable, hospice care should be sought.

Goals of Therapy

The initial goal in the management of heart failure is to relieve symptoms associated with fluid overload. The next focus of treatment is to slow disease progression. To date, no long-term clinical trials have demonstrated any mortality benefits of diuretic therapy, except for the Randomized Aldactone Evaluation Study (RALES).[16] The study, which found a 30% reduction in the risk of death and 35% reduction in hospitalizations among patients treated with aldactone compared with placebo, as well as a significant improvement in the symptoms of heart failure, included NYHA class III to IV patients with left ventricular ejection fractions (LVEF)

<35%.[16] This trial did not examine the diuretic effect but rather the impact of aldosterone antagonism with aldactone. In most clinical trials, patients are already treated with diuretics, and it becomes difficult to determine the impact of this class of agents on outcomes. Diuretics are generally first-line therapeutic agents, and furosemide is the most frequently prescribed. Diuretic dosing is based on the patient's response and is balanced by maintaining adequate renal perfusion.

ACE Inhibitors

The mainstay of heart failure management is ACE inhibition. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), which compared enalapril versus placebo in NYHA class IV patients, established ACE inhibitors as the cornerstone of heart failure management.[17] Since this study, numerous randomized, prospective placebo-controlled clinical trials involving thousands of patients have demonstrated a mortality benefit for patients with NYHA class I to IV heart failure who are treated with this class of drugs. The decrease in all-cause mortality ranges from 20% To 25%, ($P \leq 0.001$), and the decrease in the combined risk of death and hospitalization is in the order of 30% to 35% ($P \leq 0.001$).[18–22] Furthermore, ACE inhibitors have been shown to improve cardiac function, symptoms, and clinical status. Their effects on exercise tolerance are equivocal. Contraindications to the use of ACE inhibitor therapy include renal dysfunction, hyperkalemia, hypotension, and cough. Patients should be cautioned that they may experience initial dizziness or lightheadedness, which over time will improve. Despite the lack of symptomatic improvement, patients may still benefit from a reduction in progressive heart failure due to LV remodeling. An attempt is made to titrate the dose to the target doses used in the clinical trials; however, the ATLAS study, which examined the effects of low dose (2.5–5 mg) versus high dose (32.5–35 mg) lisinopril in patients with NYHA class II to IV heart failure, LVEF, 35%, revealed that patients on higher doses had an increased survival benefit. For those patients who cannot tolerate higher doses of ACE inhibitors, the mortality benefit is afforded even with lower doses.[21]

Despite the evidence favoring the use of ACE inhibitors, they are currently underutilized due to concerns with potential side effects. The survival advantage associated with ACE inhibitors is so strong that the FDA has mandated that all clinical heart failure trials now be performed on a background of treatment that includes ACE inhibitors.

β-Blockers

While ACE inhibitors block neurohormonal activation of the renin angiotensin system, data regarding the use of β-blockers for neurohormonal blockade equals or exceeds that of ACE inhibitors. The 3 β-blockers, which have been shown to improve mortality, are carvedilol, bisoprolol, and metoprolol succinate. Carvedilol, a nonspecific β-blocker, which has α, β, and antioxidant properties, has been shown to be of therapeutic benefit to patients with class I to IV heart failure. The US Carvedilol study group found a 64% relative reduction in mortality, as well as a 7.4% absolute reduction in all-cause mortality.[23–27] Toprol XL, a β-1 selective agent, has also been shown to have a mortality benefit. Kaplan-Meir survival curves from the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial, which compared long-acting metoprolol succinate to placebo in class II to IV heart failure patients, LVEF <40%, found a 35% reduction in total mortality with this select β-blocker, as well as further reductions in SCD and hospitalization (Fig. 3).[28] A similar benefit was seen with bisoprolol in the Cardiac Insufficiency Bisoprolol Study (CIBIS II). This trial examined the effects of bisoprolol compared with placebo in NYHA class III to IV patients with LVEF <40%. A 34% reduction in all-cause mortality, particularly from SCD, was seen.[29]

The Carvedilol Prospective Randomized Cumulative Survival trial (COPERNICUS), which looked at NYHA class IV heart-failure patients with ejection fractions of less than 25%, also demonstrated a 35% decrease in all-cause mortality, as well as a 24% decrease in the combined risk of death or hospitalization with carvedilol.[21] From these data, all patients with stable NYHA class II to IV heart failure should receive a β-blocker, unless their use is contraindicated.

In contrast, the Beta-blocker Evaluation of Survival Trial (BEST) found a statistically nonsignificant trend toward reduced mortality with bucindolol.[30]

The selection of the specific β-blocker to be administered remains controversial as indicated by the results of the Carvedilol Or Metoprolol European Trial (COMET), which suggested that differential benefits may be afforded by different β-blockers. In this randomized multicenter double-

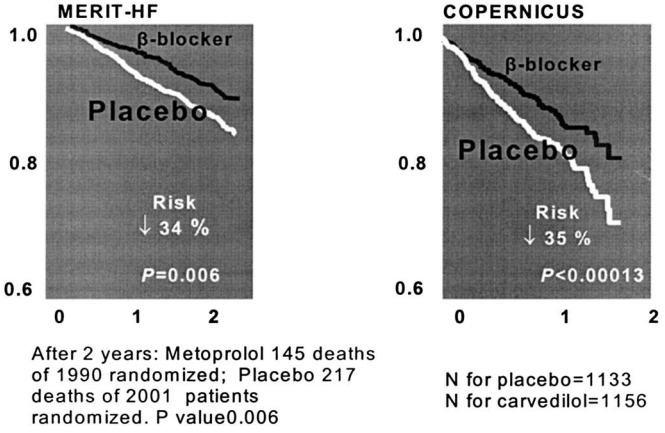

FIGURE 3. Effect of β-blockers on mortality.[28,64]

blinded trial, all-cause mortality was 34% for carvedilol and 40% for metoprolol (hazard ratio 0.83,[31] $P = 0.0017$);[31] however, there were no differences in hospitalizations. Several issues regarding the design of COMET have been raised. These include the choice of dose and dosage regimen of immediate-release metoprolol tartrate (50 mg BID), a dosage form that has never been shown to reduce mortality in patients with heart failure.[32] Additional studies are needed to fully understand whether there are any advantages of selective versus nonselective adrenergic blockade and whether there are any clinically meaningful differences in effectiveness between β-blockers with proven benefit in the management of chronic heart failure. The results of COMET demonstrate that all β-blockers and dosage forms are not interchangeable when prescribed for heart failure survival. Whether the target doses of the different β-blockers were appropriate and equivalent remains controversial.

Similar to ACE inhibitors, β-blockers are underutilized in heart failure. Most heart failure patients do not tolerate β-blockers very well initially, and these drugs have been known to precipitate heart failure. Present recommendations are that patients should be prescribed those β-blockers evaluated in the large-scale clinical trials and major efforts should be made to push the β-blocker to its maximal tolerated or target dose.

Successful initiation of β-blocker therapy in heart failure patients requires particular care. The patient should be euvolemic at the time of initiation, as, in conditions of volume overload, he/she may rapidly progress to decompensated heart failure. Patients should be seen weekly or bimonthly, and β-blocker dosages should be increased gradually and with care. In many cases, it may require up to 6 months before patients can achieve target doses of their medications. Patients must be well informed about possible side effects, as well as potential long-term benefits, since these are the key to the successful initiation and maintenance therapy with β-blockers. Finally, the physician must be persistent in maintaining a patient on β-blockade.

ARBs

If patients are intolerant of ACE inhibitors, the alternative agent is either an ARB or the combination of hydralazine with nitrates. To date, there is no evidence that ARBs are superior to ACE inhibitors in the treatment of heart failure. Initially, the Evaluation of Losartan in the Elderly (ELITE) I study, which looked at the use of Losartan compared with captopril in elderly patients (age >65) with heart failure, LVEF 40%, suggested a mortality benefit of ARBs over ACE inhibitors.[33] However, this finding was not confirmed in the subsequent larger-scale ELITE II study.[34] The international, randomized, double-blinded Valsartan in Chronic Heart Failure (VAL-HeFT) trial compared THE ARB valsartan with placebo added to the prescribed treatment of NYHA class II to IV heart failure patients, including ACE-I and β-blockers. While valsartan reduced the risk of the combined end point of all-cause mortality and morbidity by 13.2% over a 2-year follow-up, it did not improve the end point of all-cause mortality.[35] In a subgroup analysis of patients intolerant to ACE inhibitors, valsartan did confer a mortality benefit and reduced the end point of all-cause mortality by 33% and the combined end point of mortality and morbidity by 44% compared with placebo.[36] Based on these findings, valsartan became the first ARB to be approved by the US Food and Drug Administration for the treatment of New York Heart Association class II to IV HF in patients who are intolerant of ACE-inhibitors. Further post hoc analysis revealed that when more complete neurohormonal blockade was provided with the combination of ACE inhibitor, ARB and β-blocker, a trend toward increased mortality was seen, and this combination is presently not recommended.[35]

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial, which consisted of 3 discrete studies, looked at the effects of candesartan in addition to best possible treatment of heart failure.[37] CHARM-Added examined patients with left ventricular dysfunction taking ACE inhibitors, while CHARM-Alternative studied ACE intolerant patients. CHARM-Preserved was the first trial to study patients with preserved left ventricular function. While no impact on mortality was found in this group, fewer patients in the candesartan group were admitted to hospital for CHF once ($P = 0.017$) or multiple times than in the placebo group.[38] CHARM-Alternative was considered a success in that its participants experienced a significant reduction in each component of the study's primary end point, which was a composite of cardiovascular death or hospitalization for heart failure, over a median follow-up of 34 months.[39] In the CHARM-Added treatment arm, no effect on mortality was seen, but a trend toward decreased hospitalization for heart failure was noted.[40] Hence, analogous to valsartan, the ARB candesartan is an excellent alternative agent in the treatment of heart failure for ACE-intolerant patients.

The Valsartan in Acute Myocardial Infarction (VALIANT) trial examined the effects of the ARB valsartan in survivors of acute MI complicated by heart failure and/or resulting in left ventricular dysfunction. While this trial did not look specifically at patients with chronic heart failure, the investigators found that valsartan was as effective as captopril in reducing mortality in postmyocardial infarction patients with LV systolic dysfunction, HF, or both. The 2 in combination did not improve survival (Fig. 4).[41] AQ: 6

ARBs are favored over hydralazine and nitrates in ACE-intolerant HF patients. This combination is only used in patients who are ACE and ARB intolerant. The data for use of hydralazine and nitrates stems from the Vasodilator Heart Failure Trial (V-HEFT), which compared the effects of hy-

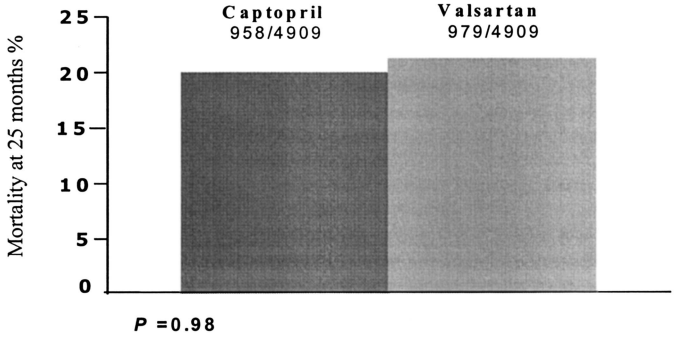

FIGURE 4. Effect of ARBs on survival in HF: The Valiant trial.[41]

dralazine and isosorbide dinitrate with those of enalapril patients receiving digoxin and diuretic therapy for heart failure. Although a survival benefit was seen in the hydralazine-isosorbide dinitrate arm, mortality after 2 years was significantly lower in the enalapril arm (18%) than in the hydralazine-isosorbide dinitrate arm (25%; $P = 0.016$). In contrast, body oxygen consumption at peak exercise was increased only by hydralazine-isosorbide dinitrate treatment ($P < 0.05$). LVEF, which increased with both regimens during the 2 years after randomization, increased more ($P < 0.05$) during the first 3 months in the hydralazine-isosorbide dinitrate group.[42]

Although ACE inhibition has been proven to be an effective therapy in the treatment of heart failure, controversy exist as to its efficacy in African Americans. Analysis of previous trials has shown that the combination of hydralazine plus nitrates may be more beneficial in African Americans with HF than Caucasians. Traditionally underrepresented in heart failure studies the African American Heart Failure Trial (A-HeFT) is the first heart failure study to focus on this population. This randomized, and placebo-controlled trial in African American patients with stable NYHA class III to IV HF compares the effects of a combination pill BiDil (fixed dose hydralazine plus isosorbide dinitrate) to placebo in addition to standard therapy.[43,44] This study was prematurely halted after a significant survival benefit emerged among patients receiving the combination pill. Further studies will need to be performed to determine the best treatment strategy for this population of patients.

Digitalis

Prior the 1990s, digoxin and diuretics were the only reliable drugs for the treatment of heart failure. However, it was not until the Digitalis Investigation Group (DIG) trial that the effects of digoxin therapy were formally studied. The results of this trial demonstrated a decrease in all-cause heart failure hospitalizations but did not demonstrate a mortality benefit from digitalis over placebo in NYHA class II to III heart failure ($P = 0.80$).[45] However, in the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED)[46] and the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) trial,[47] patients developed decompensated heart failure when digoxin was withdrawn.

Complementary Heart Failure Treatment: Device Therapy With Cardiac Resynchronization and Defibrillation

While lifestyle modification and pharmacology remain the first-line interventions for the initial presentation of heart failure or for those at risk, there are limitations to current pharmacology. Discontinuation of drug therapy due to adverse events, side effects, and noncompliance is high. Despite even the best pharmacologic management, some patients continue to have symptoms at rest, or exercise intolerance, and mortality remains high. With device therapy, compliance or a request to have the device deactivated is almost a nonissue.

More recently, CRT has been demonstrated to improve functional status and reduce hospitalizations in NYHA class III and IV patients. When used in conjunction with an ICD, cardiac resynchronization reduced all-cause mortality in advanced-heart-failure patients. A number of observational studies, as well as randomized controlled trials, have consistently demonstrated safety, efficacy, symptom benefit, as well as survival advantage with CRT.

The Multicenter InSync Randomized Clinical Evaluation, or MIRACLE, trial was the first randomized prospective clinical trial to demonstrate a benefit from CRT.[48,49] This study was not sufficiently powered to evaluate differences in mortality but showed an improvement in NYHA functional class as indicated by improved quality of life scores and 6-minute-walk testing. In addition, patients in the CRT arm had fewer hospitalizations associated with reduced length of stay in hospital and reduced requirements for intravenous medications for treatment of heart failure.

The Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial was the first adequately powered trial to compare the effects of optimal drug treatment alone versus cardiac resynchronization therapy, with or without an ICD in conjunction with optimal pharmacologic therapy, and had a primary end point of all-cause mortality and all-cause hospitalization (Table 3).[50] This landmark trial was prematurely terminated due to a nearly 20% reduction in the primary end point in the CRT arm.[51] Furthermore, this trial was the first study to demonstrate a mortality benefit of CRT-D (defibrillator) over pharmacologic therapy in HF, regardless of whether the etiology was ischemic or nonischemic.

AQ: 7
T3

SCD

SCD is also a major epidemiologic problem, occurring most frequently in post-MI patients with reduced ejection

TABLE 3. The COMPANION Trial

	All-Cause Mortality and Hospitalization	HF Mortality + Hospitalization	All-Cause Mortality
CRT-P (617)	↓ 20% ($P = 0.0002$)	↓ 34% ($P = 0.002$)	↓ 24% ($P = 0.06$)
CRT-D (595)	↓ 20% ($P < 0.001$)	↓ 40% ($P < 0.001$)	↓ 36% ($P = 0.002$)

Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350:2140–2150

fraction (EF). In 1996, Moss et al[52] demonstrated a 54% reduction in mortality among patients with a history of MI, an EF <35%, and nonsustained VT confirmed by electrophysiologic (EP) testing who received an ICD compared with patients with medical therapy alone. The follow-up Multicenter Automatic Defibrillator Implantation Trail II (MADIT II) trial established the benefit of defibrillator implantation in NYHA class II or III HF patients with history of MI, an EF <30%, who had not had an EP study.[53] This study clearly holds a promise of improved survival for the estimated more than 3 million post-MI patients with LV dysfunction.

Presently, the ACC/AHA guidelines for the evaluation and management of chronic heart failure in adults for ICD placement in post-MI patients with an EF ≤30%, either 30 days post-MI or 3 months post-CABG is a class IIa recommendation (Fig. 5). F5

While patients with ischemic cardiomyopathy clearly derive a mortality benefit from ICD therapy, it is unclear what the benefit to patients with nonischemic cardiomyopathy would be. The goal of the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE) was to determine whether ICD therapy in a background of standard medical therapy compared with standard medical therapy alone would improve survival in patients with nonischemic cardiomyopathy with LV systolic dysfunction, EF ≤35%, and frequent premature ventricular complexes or nonsustained ventricular tachycardia. After 2 years, the difference in all-cause mortality did not reach statistical significance. However, there was a significant reduction in SCD in the ICD arm ($P = 0.01$), and a reduction in all-cause mortality was seen in the subgroup of patients who were NYHA class III ($P = 0.009$).[54]

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) has finally answered this question. This trial was a 3-arm study comparing placebo to amiodarone or prophylactic ICD in patients with ischemic or nonischemic dilated cardiomyopathy. A decrease in overall mortality in patients with coronary artery disease or nonischemic cardiomyopathy who are NYHA class II or III and have an LVEF ≤35% was seen in the ICD arm. Interestingly, a survival benefit was not seen with amiodarone (Fig. 6).[55] AQ: 8 F6

Amiodarone has been demonstrated to reduce SCD in multiple post-MI trials, but not overall mortality.[56,57] Due to the high rate of SCD in cardiomyopathy patients, studies of amiodarone use had been extended to heart failure patients. Until SCD-HeFT, the 2 pivotal trials on amiodarone use in cardiomyopathy patients were the Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy (CHF-STAT) and Grupo de Estudio de la Sobrevida en lsuficiencia Cardiaca en Argentina (GESICA) trial, which had conflicting results. CHF-STAT revealed a null effect on overall survival with a trend toward improved survival in nonischemic cardiomyopathy patients,[58] whereas improved survival was seen in the GESICA trial.[59] While amiodarone could not be recommended for prophylactic arrhythmia suppression, it could be used safely in patients for whom antiarrhythmic therapy was warranted. With the completion of SCD-HeFT, guidelines will need to be established as to who will be a candidate for

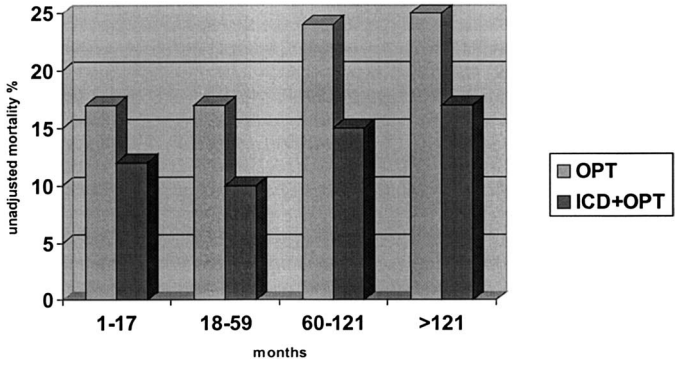

FIGURE 5. MADIT II: The benefits of an ICD are maintained.[65]

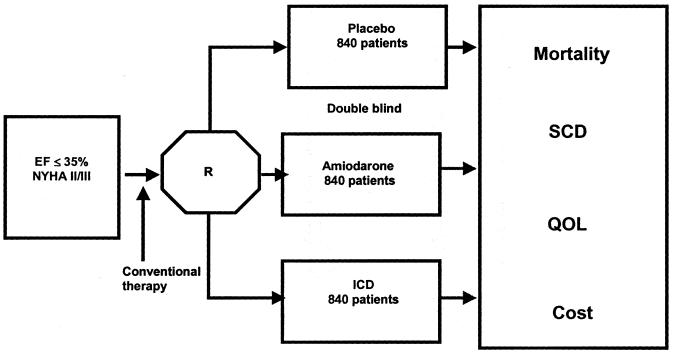

FIGURE 6.

device versus antiarrhythmic therapy as device implantation for everyone will be cost-prohibitive.

Optimizing the Management of Heart Failure

Strict adherence to a salt-restricted diet, water restriction, and persistence with initiation of ACE inhibitors or β-blockers are essential for the successful management of LV systolic dysfunction. When patients decompensate, it is usually because of inadequate dosing of diuretic medication, the deleterious effects of calcium channel blockers and NSAIDs, and a lack of compliance. Patients who suffer from refractory heart failure usually decompensate as a result of lack of ACE inhibition, the aforementioned errors, and comorbidities, such as renal failure, chronic obstructive pulmonary disease, depression, diabetes, and deconditioning. Decompensation is also caused by disease progression due to new ischemia, worsening mitral regurgitation, or arrhythmia. After a heart failure patient has been stabilized during hospital admission, approximately 30% to 60% of patients are readmitted within 6 months. Of these rehospitalizations, 50% are preventable and include noncompliance with medications, inadequate discharge planning, inadequate follow-up, or a failure with social support systems. Unfortunately, failure of the patient to seek medical attention when signs and symptoms of heart failure recur is also to blame.

In an effort to decrease hospitalizations, improved heart failure specialty programs have been developed.[60–63] The focus of these programs is on patient education and descriptive teaching of the pathophysiology of their heart failure. Emphasis is placed on adherence to prescribed dosing regimens, and instructions regarding fluid management and dietary restrictions are provided. Telephone monitoring is provided to assist with weight control and to monitor symptoms associated with worsening heart failure. Usually, if follow-up is provided within 48 hours of discharge and the patient is closely monitored, hospitalizations can be decreased.

CONCLUSION

Heart failure is a progressive disease. To date, pharmacologic therapy has led to an improvement in symptoms and may favorably affect left ventricular remodeling. Despite advances, this disease remains a growing health care problem in the United States and developed countries. Five million Americans are diagnosed with heart failure, and each year there are half a million new cases. The challenge is for clinicians of all specialties to keep "at-risk groups" in mind and to identify these patients earlier. Patients benefit from earlier intervention and counseling regarding the risk of heart failure, lifestyle modifications, and the value of pharmacologic and dietary compliance. Patients and health care providers require better education regarding the unequivocal evidence from clinical trials about the reduction in mortality and morbidity afforded by device therapy. In the 21st century, the future of heart failure management lies in the integration of pharmacologic and device therapy.

In the early 1990s, the management of acute MI was revolutionized. Teams were formed to rapidly identify and treat patients with ST-segment-elevation MI. As a result, improved survival was documented in the American Heart Association statistics for patients presenting with, being diagnosed, and surviving MI. A similar strategy can work for heart failure. Formation of care teams for early identification of patients at risk, development of algorithms and critical pathways, and practicing evidence-based medicine are all within our capabilities. Toward this end, the National Coalition for the Management of Left Ventricular Dysfunction has been formed and invites you to join in this comprehensive project to impact on the course of this epidemic at www.nclvd.org.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES 1

AQ1—LV expanded correctly? (left ventricular)

AQ2—In all table footnotes, complete reference information has been added as found on PubMed.

AQ3—Table 2 was not cited in original text, please correct or verify placement. Also, on table 2, please verify expansions in table footnote are correct for SD and LV.

AQ4—Figure 3 was not cited in original text, please correct or verify placement.

AQ10—Added reference 64 for citation here.

AQ5—Please verify reference 21 is meant here. It appears to refer to ATLAS study, not COPERNICUS.

AQ6—Figure 4 was not cited in original text, please correct or verify placement.

AQ7—Table 3 was not cited in original text, please correct or verify placement.

AQ8—Figure 6 was not cited in original text, please correct or verify placement. Also, please provide a legend for Figure 6.

AQ9—Added reference 65 for use in Figure 5 legend, please provide complete reference information (journal, pages)