



REVIEW PAPER

Advanced Heart Failure: A Call to Action

Heat failure (HF) affects more than 5 million patients in the United States and is associated with high morbidity and mortality rates.¹ Despite improvements in medical therapy with the use of angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, β -blockers, and cardiac defibrillators, more than 250,000 people die of HF each year.¹⁻⁴ Although some of these patients die suddenly with few symptoms of HF, it is estimated that between 300,000 and 800,000 patients have "advanced HF." This is defined as patients with left ventricular systolic dysfunction who experience symptoms that limit daily activity with poor exercise capacity despite maximal therapy.⁵ Recommended therapies for these patients, in addition to optimal medical management, include biventricular pacing, cardiac transplant, and mechanical circulatory support.²⁻⁴ When patients do not respond to these therapies, or cannot tolerate them, hospice and palliative care become the only option.

While there is significant clinical evidence demonstrating that advanced HF patients benefit from the recommended therapies, it is often quite difficult to determine when a patient with stable New York Heart Association (NYHA) functional class III will progress to advanced-stage HF. As shown in Figure 1, there is a continuum across which patients with HF progress. Recently, the American College of Cardiology (ACC) and the American Heart Association (AHA) developed a stage classification system for describing HF.⁶ Many patients, despite having left ventricular dysfunction, are completely asymptomatic and are classified as having stage BHF. Some of these patients, regardless of their evolution of disease will not seek or receive medical care. Others will be treated with optimal

Despite improvements in medical therapy for heart failure, more than 250,000 people die in the United States as a result of heart failure each year. There are multiple risk factors and models that have been created to identify these people, yet there has not been a significant impact on outcomes or change in the therapies for these patients. The authors review the available therapies for patients with advanced heart failure and the various risk models available to predict morbidity and mortality and present simple "office predictors" that could be used to potentially predict patients who would benefit from these therapies. Congest Heart Fail. 2008;14:316-321. © 2008 Le Jacq

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medical management and will remain stable for a period of time. Eventually, most patients progress to developing symptoms of HF and are classified as having stage CHF. Presentation will vary among patients. With time, as the left ventricle dilates further, patients will progress to advanced HF with symptoms at rest or with mild exertion, known as stage D. Patients may have periods of decompensation that require hospitalization but will then temporarily improve and become less symptomatic, fluctuating between NYHA functional class III and IV and ACC/AHA stages C and DHF. The ideal time for referral for advanced HF therapies is when the patient progresses from having stable HF to having advanced HF. Often, this referral doesn't happen until the patient is moribund or doesn't happen at all. This may occur for many reasons. Physicians may not be convinced that the advanced HF therapies available provide

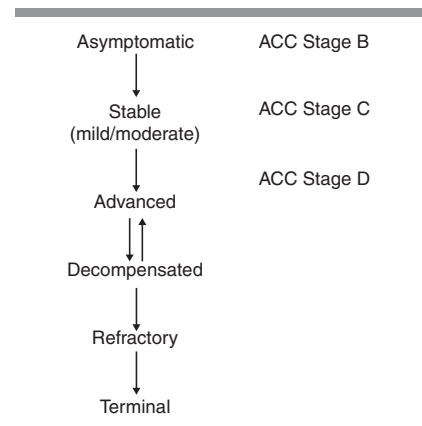


Figure 1. Progression of heart failure by American College of Cardiology (ACC) stages. Within stage D, heart failure can change between advanced and decompensated as well as progress to refractory and terminal.

superior outcomes to those they can provide without making a referral to a tertiary care center. The referring physician may not have an established referral

pathway that allows the partnership required to provide care for these complex patients. Most common, progression of HF is often quite difficult to predict and, when the progression occurs, it may happen so quickly that the patient is soon not a viable candidate for any of the advanced-stage therapies.

In this article, we have 3 goals:

- Define the current field in terms of available therapies.
- Provide guidance to referring physicians who wish to identify patient progression.
- Propose further study to validate our model/theory.

We will begin with a review of the current therapies and the corresponding outcomes available for advanced-stage HF patients. Also, based on published predictors of mortality, we offer a simple prognostic model to assist referring physicians in determining when their patients have progressed to the point at which referral for advanced-stage therapies are necessary. Finally, we propose a study to validate this model.

Therapies for Advanced HF

The ACC/AHA 2005 update for the diagnosis and management of HF approaches the treatment of HF by dividing therapies based on the patient's clinical stage of HF.⁴ Therapies vary depending on the severity of the patient's disease, as outlined in Table I. For the stage D refractory patient, optimal medical and device management includes salt and fluid restriction; use of ACE inhibitors or angiotensin receptor blockers, β -blockers, diuretics, and implantable cardioverter-defibrillators (ICDs); and, in select patients, use of aldosterone antagonists, digitalis, hydralazine/nitrates, and biventricular pacers. In addition, other therapies that should be considered include heart transplant, chronic inotropes, permanent mechanical support, and experimental surgery or medications, depending on the patient presentation and appropriateness of these options for the particular patient.

Table I. ACC/AHA-Recommended Therapy for Heart Failure Patients by Stage⁶

Stage A	ACE inhibitor or ARB in appropriate patients	
Stage B	ACE inhibitor or ARB in appropriate patients. β -Blockers in appropriate patients	
Stage C	Routine Diuretics if fluid retention ACE inhibitors β -Blockers	Select patients Digitalis Hydralazine/nitrates Biventricular pacing Implantable defibrillators
Stage D	Hospice Heart transplant Chronic inotropes Permanent mechanical support Experimental surgery or drugs	
Abbreviations: ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; AHA, American Heart Association; ARB, angiotensin receptor blocker.		

Heart Transplant. Cardiac transplant is considered a preferred therapy for appropriately selected patients with advanced-stage HF. Transplant provides strong outcomes, with a 50% survival rate at 9.9 years for all patients and a 50% survival rate of 13 years for patients who survive the initial posttransplant year.⁷ Patients return to a near-normal quality of life and functional capacity. Due to limitations in the supply of donor organs, however, only 2000 patients a year receive transplants in the United States, and it is clearly not an option for the vast majority of patients with advanced-stage HF. In addition, due to long waiting times for donor organs, more than 10% of the waiting-list patients die each year. Better therapeutic options must be sought to improve outcomes and avoid mortality for these patients.

Chronic Inotropes. Inotropes are known for their ability to increase contractility and improve symptoms in the short term but are frequently associated with a mixture of negative side effects. All inotropes can induce arrhythmias and tachycardia and activate the renin-angiotensin-aldosterone system. Despite the routine and accepted use of inotropes in patients with refractory HF, inotropes have not been extensively evaluated in this patient population. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study⁸ evaluated the use of milrinone in addition to routine medical

therapy in patients admitted with HF. Patients with predominantly NYHA III and IV symptoms were randomized to either a 48-hour infusion of milrinone or placebo. There were no differences in the number of days hospitalized within 60 days of randomization, in hospital or 60-day mortality, or the incidence of death or readmission. However, 35% of the patients were readmitted or had died within the next 60 days. This study revealed that despite an improvement in clinical status, inpatient therapy with milrinone for routine exacerbations of HF is not clinically useful. In addition, the study demonstrated that HF hospitalization is a marker of disease progression, with 8.9% of the placebo patients and 10.3% of the milrinone patients dying within the next 60 days.

This study was followed by the Continuous Outpatient Support With Inotropes (COSI) study.⁹ Thirty-six inotrope-dependent patients (defined as worsening of clinical status with attempted withdrawal) were discharged to home on long-term inotrope therapy. These patients had truly advanced-stage HF, with an ejection fraction of 19.9%, systolic blood pressure of 97 mm Hg, serum creatinine of 1.6 mg/dL, and serum sodium of 132 mEq/L. The median survival rate postdischarge was 3.4 months, and 12-month survival was 6%. Truly inotrope-dependent patients do not do well with inotropic therapy. Similar results were found from a retrospective analysis of the outcomes of patients taking inotropes in the Randomized Evaluation of Mechanical

Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial.¹⁰ In this trial that evaluated the use of ventricular assist devices as permanent therapy for patients with advanced-stage HF, 91 of 129 patients were taking inotropic therapy at the time of randomization. The survival rates in the group that received medical therapy was 24% at 1 year and 11% at 2 years.

Bridging patients to transplant on inotropes is also a commonly accepted, although minimally documented, practice. In fact, there is a mounting body of evidence that suggests that other advanced HF therapies, such as ventricular assist devices (VADs), offer better outcomes and decreased mortality. Aaronson and colleagues¹¹ reported that in a cohort of 102 patients awaiting heart transplant, overall survival of the VAD patients was superior to the inotrope group. Bhat¹² found that in 16 of 39 patients treated with an inotrope, a VAD was still needed to successfully bridge the patients to transplant. Clearly, inotropes alone should not be considered the only option for bridge to transplant and, in fact, may negatively impact outcomes if used inappropriately.

Ventricular Assist Devices. Left VADs (LVADs) have been used for nearly 30 years to support patients awaiting cardiac transplant until a suitable donor becomes available. Until recently, however, they were limited to this small group of patients. The REMATCH trial¹³ was designed to evaluate the use of an LVAD as a long-term permanent therapy for patients not eligible for a transplant. In the trial, 129 patients not eligible for cardiac transplant were randomized to either continued medical therapy or surgery with placement of an LVAD. The survival rate at 1 year was 52% in the LVAD group and only 25% in the medical therapy group. Similar improvements in survival were present at year 2. Although quality-of-life measurements all showed improvements in the LVAD arm, LVAD therapy was associated with a longer total and initial hospital stay, more infections, and more neurologic events. However, a follow-up

study demonstrated that many of these outcomes improve with improved surgical experience. Long and colleagues¹⁴ reported results in 42 patients that had an LVAD placed after the REMATCH trial, and survival at 1 year had improved to 61%. Despite this improvement, “destination” therapy has still not been widely accepted by the medical community, except in relatively isolated circumstances. In addition, a recently presented study has shown that refined patient selection is required to improve outcomes, noting that some patients receive VAD therapy at a point when they are too ill to experience an optimal outcome.¹⁵ Based on a multivariate analysis of clinical predictors of poor outcomes after placement of an LVAD, a group of very high-risk patients were identified with a greater than 90% chance of in-hospital mortality. This study demonstrates that there is a group of patients that are simply too ill for a positive outcome, thus negatively impacting the perception of destination therapy. Although there is not a limit to the number of VADs that can be implanted, as there is with transplant, there is still a need for appropriate and timely application of the technology. This validates the need for development of a simple clinical risk model to identify patients for referral to an advanced HF center when these advanced, proven therapies still have the potential for clinical benefit.

Risk Factors for Mortality in Patients Evaluated for Cardiac Transplant

There are a large number of biochemical-, structural-, physiologic-, and medical-based risk factors that have been associated with mortality in patients with HF.

The landmark Studies of Left Ventricular Dysfunction (SOLVD) trial¹⁶ was the first major study in HF to evaluate clinical predictors of mortality. From this trial, retrospective analyses have shown that elevated plasma norepinephrine levels, atrial fibrillation, renal insufficiency, reduced ejection fractions, enlarged diastolic dimensions, and

diuretic use have all been shown to be associated with an increased risk of mortality.^{17–21}

Similarly, others have developed risk models for predicting mortality in patients evaluated for cardiac transplant. Mancini and colleagues²² first evaluated the use of the metabolic exercise test to determine whether the use of peak oxygen consumption can help to predict mortality. They found a direct relationship between lower peak oxygen consumption values and mortality. In addition, they found that patients with peak oxygen consumption ≤ 14 mL/kg/min had a survival advantage with cardiac transplant compared with continued medical therapy. Since that landmark paper in 1992, peak oxygen consumption has been used to determine whether patients should be listed for transplant. This work was later advanced by the Heart Failure Survival Score (HFSS).²³ Aaronson and colleagues²³ developed a risk model for HF patients and identified low-, medium-, and high-risk groups. Risk factors for mortality included an ischemic etiology, higher heart rates, lower ejection fraction and mean blood pressure, presence of an intraventricular conduction delay, peak oxygen consumption, hyponatremia, and elevated pulmonary capillary wedge pressures. While simple, variables such as oxygen consumption and pulmonary capillary wedge pressures are rarely obtained unless a patient is being evaluated for cardiac transplant and therefore rarely assist in determining when someone is ready for referral. There is still a need for help in determining when patients should be referred for advanced therapies.

Risk Factors for Mortality in Patients With HF

Table II outlines a number of studies that have been performed in both the inpatient and outpatient settings to assist in determining prognosis in patients with HF.^{24–39} Although the modeling methods that were performed, the exact variables evaluated, and length of follow-up varies from study to study, a consistent pattern of results are

Table II. Markers of Mortality in Studies Evaluating Prognosis in Patients With Heart Failure

AUTHORS	PATIENT TYPE	No.	MARKERS	1-YEAR SURVIVAL RATE, %
Chin et al ²⁴	In	257	BP <100 mm Hg, DM, nonsinus rhythm	N/A
Alla et al ²⁵	In	301	HR >100 beats per minute, Na <134 mEq/L, Creat >2.0 mg/dL, age >70 y, prior hosp	57.6
Cowie et al ²⁶	In	220	Age, crackles on examination, low BP, high Creat	62
Jong et al ²⁷	In	38,702	Male; age; malignancy; dementia; renal, cerebrovascular, rheumatologic, peripheral vascular, or pulmonary disease; ischemic etiology, DM	66.9
Bouvy et al ²⁸	In	152	DM, high Creat, NYHA III/IV, low BMI, low BP, edema	N/A
Lee et al ²⁹	In	4031	Age, low BP, high RR, high BUN, low Na	69.5
Kittleson et al ³⁰	In	259	No ACE, low BP, low Na, high Creat	N/A
Felker et al ³¹	In	949	Age, low BP, NYHA IV, high BUN, low Na	N/A
Fonarow et al ³²	In	37,772	BUN >43 mg/dL, systolic BP <115 mm Hg, Creat >2.75 mg/dL	N/A
Rector et al ³³	In	769	Age, low BP, low Hgb, low Na, high BUN	50% (high risk)
Rohde et al ³⁴	In	779	Cancer, systolic BP <124 mm Hg, Creat >1.4 mg/dL, BUN >37 mg/dL, Na <136 mEq/L, age >70 y	N/A
Mahon et al ³⁵	Out	585	Low Creat cl, 6 MW <262 m, low EF, recent hosp, diuretic	
Eshaghian et al ³⁶	Out	1354	Low EF, low Na, low Hgb, high BUN, high Creat, diuretic dose	
Greenberg et al ³⁷	Out	4280	NYHA III/IV, HF hosp, angina	
Levy et al ³⁸	Out	1125	Diuretic dose, low BP, % lymph, Hgb <16 g/dL, ischemic etiology, EF, low cholesterol, high uric acid/allopurinol use, Na <138 mEq/L, NYHA, age, male sex	
Teuteberg et al ³⁹	Out	160	High BUN, Creat, low Na, low Hct, recent hosp, no ACE/BB	

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; BB, β -blocker; BMI, body mass index; BP, blood pressure; BUN, serum urea nitrogen; Creat, serum creatinine; Creat cl, creatinine clearance; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; Hct, hematocrit; Hgb, hemoglobin; hosp, hospitalization; HR, heart rate; lymph, lymphocytes; Na, serum sodium; N/A, not available; NYHA, New York Heart Association; RR, respiratory rate; 6 MW, 6-minute walk.

reported. Evidence of poor perfusion to end organs manifested by decreased renal function, neurohormonal upregulation manifested by hyponatremia, poor exercise tolerance manifested by both NYHA functional class and 6-minute walk distance, hypotension, high diuretic doses, inability to tolerate either an ACE inhibitor or a β -blocker, and recent hospitalizations are repeatedly demonstrated to be markers of poor patient outcomes. Many of these studies have developed sophisticated models using risk scores or dividing patients into risk groups based on scores that are quite beneficial academically but, similar to the HFSS, are not used practically. Furthermore, a proven, reliable, simple clinical risk score classification that can be calculated from memory to predict mortality during the next year has never been developed, especially in the outpatient setting, despite multiple studies that have examined various risk factors for mortality.

As shown in Table III, we propose a simple group of clinical markers that,

when present in patients, should predict poor outcomes during the next year, and their presence should trigger consideration for a referral to an advanced HF center for advanced medical and surgical therapies not available in the community. All of these indicators are noted during a routine clinical visit and laboratory evaluation and would not require additional testing. Although no prognostic studies have been performed to evaluate the predictive value of these variables, based on the studies in Table II, it is quite clear that all of these variables have been shown to predict survival in large patient populations. Furthermore, a prospective trial evaluating a number of similar risk factors should be performed. Despite multiple retrospective studies of predictors, a prospective study specifically designed to evaluate risk factors for mortality in patients with HF has never been performed. The following factors should be included in such a study.

Exercise Tolerance. Bouvy,²⁸ Felker,³¹ Mahon,³⁵ Greenberg,³⁷ Levy,³⁸ and

Table III. Clinical Risk Factors for Mortality

Walk <1 block without dyspnea
Sodium <136 mEq/L
Serum urea nitrogen >40 mg/dL or creatinine >1.8 mg/dL
Can't tolerate ACEI/ARB/BB
Diuretic dose >1.5 mg/kg/d
Heart failure admission in the past 6 months
No clinical improvement with CRT therapy or no CRT and QRS >140 ms
Hematocrit <35%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker; CRT, cardiac resynchronization therapy.

colleagues all included either 6-minute walk distance or NYHA functional class in their prognostic models. We believe that the clinically relevant "how far can you walk before becoming short of breath" question reflects this evaluation in a practical manner. In addition, Stewart and colleagues⁴⁰ presented a study at the 2006 AHA Annual Meeting in which they asked patients at what point

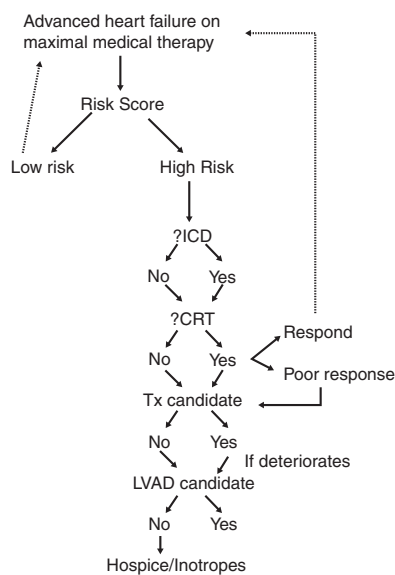


Figure 2. Flowchart of the various options and considerations that should be made for nonmedical therapy in patients with advanced heart failure. CRT indicates cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; Tx, transplant.

would they consider an LVAD. Just over 40% stated that they would consider such a therapy when they couldn't walk a block. Clearly, using exercise tolerance as a marker of functional status identifies a patient group that is willing to undergo the therapies provided at an advanced HF center and defines a group that would also benefit from the therapy.

Laboratory Evaluation. Numerous studies have included either low sodium and hematocrit values or high creatinine and serum urea nitrogen values in their prognostic values.^{19,23,25,26,28–36,38,39} The majority of these studies used the absolute value of these numbers in their model, which makes it difficult to

choose a simple value. The numbers chosen in this model, however, reflect abnormal values that fall within a range that has been shown to be predictive of events.

Medication. The inability to tolerate medications appears to be a very significant marker for predicting poor outcomes. Thirty-five percent of the patients who died in the Teuteberg experience could not tolerate an ACE inhibitor and only 38% were on a β -blocker.³⁹ Similarly, the Seattle Heart Failure Model (SHFM) demonstrates the effects of intolerance of these medications.³⁸ Conversely, the presence of a diuretic and the absolute dose of a diuretic have also been shown to be predictive of worse outcomes.^{21,35,36,38} Based on data from the SHFM, we decided on a furosemide equivalent dose of 1.5 mg/kg/d as a marker of high-dose diuretic use.

HF Admissions. Admission to the hospital for HF exacerbation has a 30% to 50% mortality rate during the next year.^{35,37,39} Clearly this is a very important marker of progression of disease and reflects a group of patients with worse outcomes.

CRT Therapy. Cardiac resynchronization therapy (CRT) improves quality of life and survival in patients with NYHA functional class III and IV symptoms and is now indicated as a therapy in patients who have a QRS width >0.12 .⁵ Recently, Saxon and colleagues⁴¹ evaluated predictors of sudden cardiac death and appropriate shock in patients who had both an ICD and CRT. They found that NYHA functional class IV patients and worsening renal function predicted appropriate

ICD therapy. In addition, appropriate ICD therapy was associated with the risk of death or all-cause hospitalization. Patients who do not clinically respond to this therapy and continue to be very symptomatic should be thought of as having a high risk for poor outcomes.

Call to Action

Despite significant improvements in current HF therapies, HF continues to be the number one discharge diagnosis in the United States each year and is associated with significant mortality. A number of risk models have been developed to predict patients with poor outcomes, but they are rarely used because of their complexity. A simple prognostic model that includes variables routinely obtained at clinical visits is required so that practitioners can quickly identify and refer patients with advanced HF symptoms before they decompensate to the point that only desperation therapies are available. Risk factors such as those shown in Table III should be used to determine whether a patient with NYHA functional class III or IV symptoms should be referred for evaluation to an advanced HF center. Using the flow chart shown in Figure 2, those patients can then be directed to the appropriate therapy. In addition, a prospective validation study using simple risk factors that can be easily obtained and used in daily practice is necessary to further advance the care of these patients.

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