Advanced (Stage D) Heart Failure: A Statement From the Heart Failure Society of America Guidelines Committee

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ABSTRACT

We propose that stage D advanced heart failure be defined as the presence of progressive and/or persistent severe signs and symptoms of heart failure despite optimized medical, surgical, and device therapy. Importantly, the progressive decline should be primarily driven by the heart failure syndrome. Formally defining advanced heart failure and specifying when medical and device therapies have failed is challenging, but signs and symptoms, hemodynamics, exercise testing, biomarkers, and risk prediction models are useful in this process. Identification of patients in stage D is a clinically important task because treatments are inherently limited, morbidity is typically progressive, and survival is often short. Age, frailty, and psychosocial issues affect both outcomes and selection of therapy for stage D patients. Heart transplant and mechanical circulatory support devices are potential treatment options in select patients. In addition to considering indications, contraindications, clinical status, and comorbidities, treatment selection for stage D patients involves incorporating the patient's wishes for survival versus quality of life, and palliative and hospice care should be integrated into care plans. More research is needed to determine optimal strategies for patient selection and medical decision making, with the ultimate goal of improving clinical and patient centered outcomes in patients with stage D heart failure. (*J Cardiac Fail 2015;21:519–534*)

Key Words: Heart failure, advanced, stage D.

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The contemporary perspective of heart failure emphasizes the progressive nature of the disease through clinically identifiable stages.[1] Stage D heart failure describes advanced progression of the heart failure syndrome characterized by structural abnormalities of the heart and severe resting symptoms despite optimal medical, surgical, and device therapy. The terms "stage D" and "advanced" are used interchangeably in the present document. Although a discussion of advanced heart failure in this context has traditionally been limited to those suffering from severe myocardial systolic dysfunction, or heart failure with reduced ejection fraction (HFrEF), our understanding of heart failure with preserved ejection fraction (HFpEF) has recently evolved. Although the latter is likely a compendium of disorders for which even the natural history remains unclear and the optimal treatment strategy unresolved, there are clearly patients with HFpEF who meet the definition of stage D.

Identification of patients in stage D is a clinically relevant undertaking because treatments are limited, morbidity is progressive, and survival is short. Recognition or acknowledgement of advanced heart failure may be elusive for patients, families, and even providers, because the signs and symptoms are often chronic, insidious, and nonspecific. Late recognition, and therefore late referral, of stage D patients limits therapeutic options, because the ability to survive advanced therapies, such as heart transplantation or mechanical circulatory support (MCS) implantation, is predicated on the overall physiologic, nutritional, and psychosocial status of the patient. Patients can also present acutely with stage D heart failure (eg, acute myocardial infarction with cardiogenic shock or fulminant myocarditis). Such patients are quite different from chronic heart failure patients that gradually progress to stage D, but they are equally if not more clinically challenging owing to limited data to guide clinical decision making.

With the advent of specialty training in advanced heart failure and recognition of this expertise,[2] there is a clear need to reassess the current state of the field. In the present statement, we review the current status and understanding of stage D heart failure, with particular emphasis on patient assessment, triggers for timely referral, treatment options, and research priorities.

Epidemiology and Survival

Data are scarce regarding the epidemiology of stage D heart failure. Data from Olmstead County, Minnesota, suggests that <1% of patients with heart failure are in stage D.[3] Worldwide data are not available. When HFrEF reaches stage D, patients are subject to exceptionally high mortality. In the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, stage D patients who were treated medically experienced 75% mortality at 1 year and virtually no survival at 2 years.[4] Optimally treated patients in the Investigation of Non–Transplant-Eligible Patients Who Are Inotrope Dependent (INTREPID) trial had survival rates of 22% at 6 months and 11% at 1 year.[5] In a random population-based sample from Olmstead County, stage D heart failure was associated with only 20% 5-year survival.[3] Patients bridging to end of life on continuous inotropes have the poorest survival: 6% at 1 year.[6]

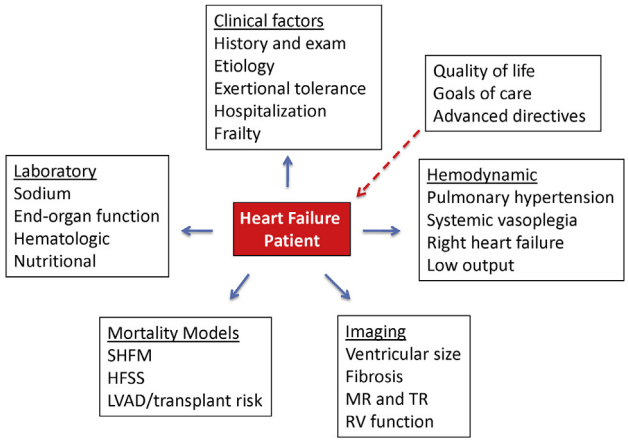

Fig. 1. Assessment domains in advanced (stage D) heart failure. SHFM, Seattle Heart Failure Model; HFSS, Heart Failure Survival Score; LVAD, left ventricular assist device; MR, mitral regurgitation; TR, tricuspid regurgitation; RV, right ventricular.

Defining Advanced Heart Failure

A precise definition of advanced heart failure is important, but it has proven to be difficult because heart failure progression is highly variable and the exact course is uncertain.[7] One can debate whether advanced heart failure should be primarily defined by subjective signs and symptoms, mortality risk, or other more objective variables, such as imaging assessments, biomarkers, and hemodynamics (Fig. 1). Symptoms can be nonspecific and do not necessarily correlate with mortality risk. Attempts to characterize heart failure progression are relevant for describing populations, but they remain too imprecise for assessment of individual patients.[8–10] Current prognostic models are limited by the interpatient variability of heart failure progression, which impairs the applicability of derivation samples and validation in specific patient cohorts. Defining advanced heart failure based on mortality risk is also difficult because there is no consensus on the expected survival that defines advanced.

Various definitions and indicators have been proposed for advanced heart failure (Table 1).[1,11–13] There is usually no single event that defines a patient as having advanced or stage D heart failure. Rather, a pattern of clinical characteristics should suggest that a patient has become refractory to traditional therapies. These characteristics include repeated hospitalizations for heart failure, intolerance or reduction of doses of neurohormonal antagonists, escalation of diuretics, development of end-organ dysfunction, malnutrition (or cardiac cachexia), and refractory arrhythmias with or without device shocks.[1] These "triggers" can identify the

Table 1. Definitions and Indicators of Advanced Heart Failure

European Society of Cardiology[12]	American College of Cardiology Foundation/American Heart Association[1,11]	Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)[13]
1. Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV) 2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or of reduced cardiac output at rest (peripheral hypoperfusion) 3. Objective evidence of severe cardiac dysfunction, shown by ≥1 of the following: a) Low LVEF (<30%) b) Severe abnormality of cardiac function on Doppler-echocardiography with a pseudonormal or restrictive mitral inflow pattern; c) High cardiac filling pressures (mean PCWP >16 mm Hg, and/or mean RAP >12 mm Hg by pulmonary artery catheterization) d) High BNP or NT-proBNP plasma levels, in the absence of noncardiac causes 4. Severe impairment of functional capacity shown by one of the following: a) Inability to exercise b) 6-MWT distance ≤300 m in women and/or patients aged ≥75 y c) Peak VO_2 <12−14 mL kg^{-1} min^{-1} 5. History of ≥1 heart failure hospitalization in the past 6 mo 6. Presence of all the previous features despite "attempts to optimize" therapy, including diuretics, RAAS inhibitors, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated	1. Repeated (≥2) hospitalizations or ED visits for HF in the past year 2. Progressive deterioration in renal function (eg, rise in BUN and creatinine) 3. Weight loss without other cause (eg, cardiac cachexia) 4. Intolerance of ACE inhibitors because of hypotension and/or worsening renal function 5. Intolerance of beta-blockers because of worsening HF or hypotension 6. Frequent systolic blood pressure <90 mm Hg 7. Persistent dyspnea with dressing or bathing requiring rest 8. Inability to walk 1 block on level ground because of dyspnea or fatigue 9. Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg and/or use of supplemental metolazone therapy 10. Progressive decline in serum sodium, usually to <133 mEq/L 11. Frequent ICD shocks	1. Profile 1 (Critical Cardiogenic Shock): Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. 2. Profile 2 (Progressive Decline): Patient with declining function despite intravenous inotropic support, may be manifested by worsening renal function, nutritional depletion, or inability to restore volume balance. Also describes declining status in patients unable to tolerate inotropic therapy. 3. Profile 3 (Stable but Inotrope Dependent): Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support because of recurrent symptomatic hypotension or renal dysfunction. 4. Profile 4 (Resting Symptoms): Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during ADL. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between profiles 4 and 5. 5. Profile 5 (Exertion Intolerant): Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may be more at risk than in profile 4 and require definitive intervention. 6. Profile 6 (Exertion Limited): Patient without evidence of fluid overload is comfortable at rest, and with ADL and minor activities outside the home, but fatigues after the 1st few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak VO_2, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment. 7. Profile 7 (Advanced NYHA functional class III): A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.

ACE, angiotensin-converting enzyme; ADL, activities of daily living; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; ED, emergency department; HF, heart failure; ICD implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NT, N-terminal; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; RAAS, renin-angiotensin-aldosterone system; RAP, right atrial pressure; 6-MWT, 6-minute walk test; VO_2, oxygen consumption.

Table 2. Indicators of Advanced Heart Failure That Should Trigger Consideration of Referral for Evaluation of Advanced Therapies*

- Need for intravenous inotropic therapy for symptomatic relief or to maintain end-organ function
- Peak VO_2 <14 mL kg^{-1} min^{-1} or $<50\%$ of predicted
- 6-minute walk distance <300 m
- ≥ 2 HF admissions in 12 mo
- >2 unscheduled visits (eg, ED or clinic) in 12 mo
- Worsening right heart failure and secondary pulmonary hypertension
- Diuretic refractoriness associated with worsening renal function
- Circulatory-renal limitation to RAAS inhibition or beta-blocker therapy
- Progressive/persistent NYHA functional class III–IV symptoms
- Increased 1-y mortality (eg, 20%–25%) predicted by HF survival models (eg, SHFM, HFSS, etc.)
- Progressive renal or hepatic end-organ dysfunction
- Persistent hyponatremia (serum sodium <134 mEq/L)
- Recurrent refractory ventricular tachyarrhythmias; frequent ICD shocks
- Cardiac cachexia
- Inability to perform ADL

SHFM, Seattle Heart Failure Model; HFSS, Heart Failure Survival Score; other abbreviations as in Table 1.
*In the setting of optimal medical and electrical therapies.
Adapted from: Stewart GC, Givertz MM. Mechanical circulatory support for advanced heart failure: patients and technology in evolution. Circulation 2012; 125:1304–15.

patient who is getting worse despite heart failure therapy (Table 2).[14] Recognizing these triggers early and initiating referral for advanced therapy evaluation is essential and may affect a patient's candidacy for such therapies, which could influence survival.

Taking into consideration the above issues, we propose that stage D advanced heart failure be generally defined as the presence of progressive and/or persistent severe signs and symptoms of heart failure despite optimized medical, surgical, and device therapy. It is generally accompanied by frequent hospitalization, severely limited exertional tolerance, and poor quality of life, and it is associated with high morbidity and mortality. Importantly, the progressive decline should be primarily driven by the heart failure syndrome (Box 1). Although broad, this definition allows for consideration of early referral, a critical step in the care of these patients. This definition should be used in conjunction with the "triggers" outlined in Table 2 to help the clinician to identify the transition of the heart failure patient into advanced stages.

Defining Failure of Optimal Medical, Device, and Surgical Therapy

Defining the failure of medical and device therapies (Table 2) in patients with heart failure is difficult, and a review of a patient's therapies by a heart failure specialist may be necessary. The first step in the assessment is to confirm that the patient's conventional heart failure management has been maximized and that reversible factors (eg, ischemia, alcohol) have been addressed. Guideline-directed medical therapy (GDMT) should be dosed appropriately, volume status optimized, and cardiac resynchronization therapy (CRT) and arrhythmia management reviewed. Comorbidities such as diabetes, sleep apnea, hypertension, atrial fibrillation, and chronic obstructive pulmonary disease (COPD) should also be addressed. Importantly, surgical or procedural therapies such as valve repair or replacement, coronary artery bypass, and aneurysmectomy should be entertained if indicated and feasible. In most cases, these discussions will require an experienced multidisciplinary team to address potential options, the impact of the proposed surgery on possible future operations, and/or the risks and benefits of deferring advanced therapies such as MCS or transplantation. Some patients referred for advanced therapies may be eligible for alternate, albeit high-risk, interventions.

Box 1. Heart Failure Society of America Definition of Advanced (Stage D) Heart Failure

The presence of *progressive and/or persistent* severe signs and symptoms of heart failure despite optimized medical, surgical, and device therapy. It is generally accompanied by frequent hospitalization, severely limited exertional tolerance, and poor quality of life and is associated with high morbidity and mortality. Importantly, the progressive decline should be primarily driven by the heart failure syndrome.

An often underappreciated indicator of advanced heart failure is the lack of response to or intolerance of heart failure therapies. Patients who require high diuretic doses, especially those on 160 mg furosemide per day or higher, have poor survival,[15] as do those who have been withdrawn from beta-blocker or renin-angiotensin-aldosterone system (RAAS) antagonists, or who require reductions in dose of either agent.[16,17] Failure to improve after CRT is another adverse marker.[18] Heart failure hospitalization despite GDMT also portends reduced survival, and recurrent hospitalizations usually suggest heart failure progression.[19]

From the patient's point of view, failure of traditional heart failure therapies is characterized by persistent moderate to severe symptoms, but the symptoms may be nonspecific, especially in older patients.[20] Specific questions to estimate functional capacity should be used. Patients who cannot walk 1–2 blocks or who cannot do a moderate

amount of yard or house work (because of heart failure as opposed to other causes, such as COPD, obesity, deconditioning, or advanced age) would be estimated to be unable to perform 4 metabolic equivalents or a level consistent with severe impairment on cardiopulmonary exercise testing.[14] Such degrees of impairment should prompt referral for more formal testing and risk stratification.[21]

Clinical status can be objectively assessed with the use of hemodynamic and functional studies. Routine use of right heart catheterization for inpatient heart failure management has not been shown to affect overall outcomes,[22] but it may be useful in a subset of patients to assess the need for inotropic support as a bridge to MCS, transplantation, or end of life (Table 3).[22,23] In this setting, right heart catheterization benefits from involvement of physicians with special expertise in advanced hemodynamic assessment, and often includes physiologic and/or pharmacologic challenges as well as recognition of limitations associated with hemodynamic measurements. Functional capacity assessed by submaximal or maximal exercise testing has been shown to predict short-term mortality and the need for advanced therapies. A 6-minute walk distance <300 m has generally been consistent with advanced heart failure and short-term mortality risk.[24,25] Multiple studies have validated the measurement of peak oxygen consumption (VO_2) to stratify patients for advanced heart failure therapies such as MCS and transplantation. In the contemporary era, a peak VO_2 of $\leq 10-12$ mL kg^{-1} min^{-1} has defined a group of patients that have improved outcomes with surgical options rather than ongoing medical management.[26,27] However, many older frail patients may not be able to perform the peak VO_2 test or even the 6-minute walk test owing to comorbid conditions or "frailty."

Biomarkers and clinical laboratory data (eg, natriuretic peptides, troponin) may also suggest progression of heart failure despite optimal management. Elevation of B-type natriuretic peptide (BNP) at admission or in follow-up and/or failure of BNP to fall with heart failure management suggests higher mortality risk.[28,29] Persistent hyponatremia (serum sodium ≤ 134 mEq/L) is associated with a doubling of the mortality rate at 6 months.[30] Elevation of the blood urea nitrogen (>30 mg/dL) is the strongest renal predictor of in-hospital and 1-year post-discharge death rates.[31]

A number of risk prediction models aim to integrate these various "markers" into quantitative scores to help characterize disease severity and risk for adverse events. Such models may help to characterize a subgroup of heart failure patients with limited short-term survival that would be classified as stage D. The Seattle Heart Failure Model (SHFM) predicts 1-year survival and allows clinicians to model the effects of clinical events and therapies that may be useful in defining patients suitable for MCS.[10,32] The Heart Failure Survival Score, which includes peak VO_2 in addition to clinical parameters and predicts survival better than peak VO_2 alone, is similar to the SHFM.[33,34] Hospitalized patients are at particular risk for short-term mortality and may represent failure of medical and device therapies. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) Risk Model and Discharge Score used 8 clinical variables to predict 6-month mortality in patients admitted for acute heart failure.[35] The Enhanced Feedback for Effective Care (EFFECT) study derived a multivariable risk model using vital signs, routine laboratories, and comorbidities at the time of admission to predict 30-day and 1-year mortality.[36]

Natural History

The interplay of neurohormonal activation, inflammation, and myocardial remodeling in the pathophysiology of heart failure has been well described.[37–40] In HFrEF, this insidious, variable, and persistent process ultimately overwhelms the benefits of conventional heart failure therapy and the disease progresses to an advanced stage. Advanced heart failure is characterized by increasing inability to meet the metabolic demands of end organs and skeletal muscle, resulting in renal and hepatic insufficiency and reduction in functional capacity, cachexia, and fatigue. End-organ dysfunction increases the mortality associated with heart failure and can potentially preclude application of advanced heart failure therapies. It should be emphasized that the clinical course of advanced heart failure is highly variable, making it difficult to precisely predict the prognosis of an individual patient.

Renal Consequences

Cardiorenal syndrome represents a spectrum of renal disease associated with poor cardiac function and can occur as a result either of acute cardiac dysfunction or shock resulting in acute deterioration of renal function or of chronic heart disease leading to chronic and progressive renal dysfunction. More than 60% of patients admitted to the hospital with acute heart failure have at least moderate

Table 3. Criteria for Home Inotrope Infusion Therapy

- Clear demonstration of both symptomatic and hemodynamic benefit from the inotrope infusion (20% improvement in cardiac index or reduction in pulmonary capillary wedge pressure)
- Attempts to optimize noninotropic medications, including the use of vasodilators and optimization of volume status, have been performed
- Attempts to wean the inotropes have resulted in worsening of symptoms
- Patient has been determined to not be a candidate or to not desire ventricular assist device implantation or heart transplantation
- There has been a detailed discussion of patient goals that describes the home inotrope infusions as a tool to facilitate discharge home and improve functional capacity but not as a measure to improve survival.

chronic kidney disease (eg, estimated glomerular filtration rate <60 mL/min).[41]

Hemodynamic stresses that occur in advanced heart failure cause dysregulation of the neurohormonal and hemodynamic balance between the kidney and heart. Renal arteriolar vasoconstriction occurs in the setting of low cardiac output and propagates a vicious cycle with increasing central venous renal back pressure, further contributing to renal hypoperfusion. Increased central venous pressure is independently associated with renal dysfunction and poor outcomes.[42,43] The end result is activation of the sympathetic nervous system and RAAS, up-regulation of inflammatory cytokines and adenosine, sodium retention, and hypervolemia. The degree of impairment tolerable for advanced therapies and/or determining the reversibility of renal dysfunction are common dilemmas in advanced heart failure management and remain unresolved.

Cardiohepatic Interactions

Cardiohepatic abnormalities have recently gained greater attention in advanced heart failure, owing in large part to the morbidity and mortality of cardiac surgery in the presence of liver disease. Abnormal liver function tests were observed in 46% of patients with advanced heart failure requiring inotropic support.[44] Both hepatocellular (ie, aspartate aminotransferase, alanine aminotransferase) and cholestatic (ie, alkaline phosphatase, bilirubin) patterns of liver injury are common. Elevations in alkaline phosphatase appear to coincide with evidence of systemic congestion and elevated filling pressures, whereas elevations in the transaminases appear to be associated with hypoperfusion.[45,46] Cardiohepatic interactions can be grouped broadly into 3 categories: 1) congestive hepatopathy, 2) acute cardiogenic liver injury (ischemic hepatitis), and 3) bridging fibrosis (cardiac cirrhosis).[47] Liver biopsy can be safely used to resolve the degree of irreversible liver injury and should be considered in operative planning.[44]

Right Ventricular Failure and Pulmonary Hypertension

Right ventricular (RV) failure is an important complication of advanced heart failure and is associated with increased mortality, particularly when combined with pulmonary hypertension.[48–50] Compared with heart failure patients with increased pulmonary artery pressure (PAP) and preserved RV function, those with elevated PAP and RV dysfunction had 4.3-fold higher mortality.[51] RV failure is more common in nonischemic cardiomyopathy and likely a reflection of both the intrinsic cardiomyopathy affecting the right heart as well as the hemodynamic load of LV failure. However, RV failure can occur in any patient with heart failure,[52,53] and when moderate to severe, can limit the outcomes of left ventricular assist device (LVAD) therapy. RV failure after implantation is associated with worse outcomes compared with patients without RV failure.[54,55] RV function should always be optimized before LVAD implantation and is critical to successful outcomes.

RV failure in advanced heart failure is a consequence of increased afterload (eg, increased pulmonary venous pressure and pulmonary vascular resistance), excessive preload (eg, high central venous pressure), and contractile dysfunction (eg, septal wall dysfunction, intrinsic muscle disease) and is exacerbated by tricuspid regurgitation.[56] Although the pulmonary hypertension associated with left heart failure may be "reversible" in its early stages, nitric oxide, endothelin, and prostaglandin dysregulation ultimately contribute to pulmonary vascular remodeling over time. In this setting, a precapillary elevation in pulmonary pressures may not be acutely reversible with heart failure management, owing to increases in pulmonary vascular resistance and transpulmonary gradient.[57] An increased diastolic pulmonary gradient (DPG) >5 mm Hg suggests concomitant pulmonary vascular disease as a contributor to pulmonary hypertension in heart failure.[58] The presence of pulmonary hypertension (PH) superimposed on left heart disease, whether passive or "mixed,"[59] is associated with decreased survival.[60,61] The presence of mixed PH, as defined by DPG ≥ 7 mm Hg and total (or trans) pulmonary gradient >12 mm Hg, may identify a group of patients with markedly reduced survival similar to that of patients with precapillary PH.[61]

Determining reversibility of PH in stage D heart failure is essential in guiding therapy.[59] Patients with irreversible precapillary PH may develop RV failure after heart transplantation and therefore may not be optimal candidates.[59]

Therapeutic Approaches

Matching Intervention to Patient Versus Populations

Clinical decisions are based on large randomized trials. However, many stage D heart failure patients do not match clinical trial populations owing to age or comorbidities. Furthermore, survival or benefit in a population does not necessarily reflect outcomes in an individual patient. Some interventions, such as MCS, are a choice between a low short-term risk/poor long-term outcomes strategy (ie, medication management until eventual death) versus a higher short-term risk/improved long-term outcomes scenario of aggressive intervention (ie, surgical MCS implantation). For each intervention, clinicians should have a realistic understanding of the potential risks and benefits and work with the patient and family to make optimal decisions. A multidisciplinary team that includes advanced heart failure clinicians, cardiothoracic surgeons, and palliative care specialists is necessary to making these decisions (Fig. 2).

Cardiac Resynchronization Therapy

Although CRT has strong evidence of benefit in HFrEF, patients with advanced heart failure have accounted for only $\sim$4% of the patients in CRT clinical trials.[62] CRT implantation in patients not likely to improve is associated with several risks, including procedural risks, device infection, risk of delay in transplantation referral, and cost.[63] In

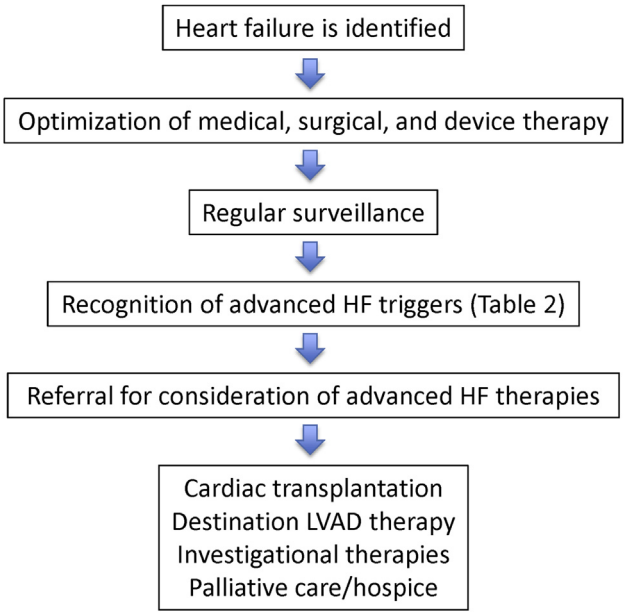

Fig. 2. A clinical approach to advanced (stage D) heart failure (HF). LVAD, left ventricular assist device.

one series, 545 of 729 CRT patients met ≥3 cardiac criteria for heart transplantation.[64] The observed 92% and 77% survival rates at 1 and 3 years, respectively, rivaled or exceeded expected transplantation outcomes. The morphologic nonresponder (defined as left ventricular [LV] end-diastolic diameter values greater than baseline or functional deterioration) rate of 21% was similar to that observed in the large randomized trials of CRT. Of note, patients who did not demonstrate reverse remodeling at 6 months after CRT implantation had more events (heart failure death, ventricular assist device implantation, or listed for transplantation). In a subset of patients with ambulatory New York Heart Association (NYHA) functional class IV heart failure enrolled in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, CRT and CRT-defibrillator therapy delayed the time to all-cause mortality and hospitalization with a trend for improvement in survival.[65]

The likelihood of benefit is less certain in patients who are inotrope dependent. In a limited case series of 10 inotrope-dependent patients, 9 were able to wean from inotropes after CRT and 7 survived without transplantation to 3 years.[66] In contrast, another series of 10 inotrope-requiring patients observed 50% mortality despite early symptomatic improvement after CRT, with a median time to death of only 6 months. These data raise concern about the cost-benefit ratio and appropriateness of "bail-out" CRT therapy in this population.[67] Patients with marked LV dilation and less dyssynchrony were noted to have poor reverse remodeling and survival after CRT.[68]

Although there is not enough evidence to conclude that CRT implantation in stage D heart failure is inappropriate, the decision should be factored into the overall goals and plan of care for each patient. For example, the potential for benefit from CRT that requires a surgically placed epicardial lead in an advanced heart failure patient must be weighed against the risk of nonresponse, perioperative morbidity and mortality, and impact on subsequent cardiothoracic procedures. Failure to improve after CRT implantation should be recognized as a serious adverse prognostic factor.

Implantable Cardioverter-Defibrillators

An implantable cardioverter-defibrillator (ICD) may abort death, but it does not improve symptoms. Aside from concomitant CRT, an ICD will not necessarily improve quality of life and is not disease modifying. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), although ICDs significantly reduced mortality, the effect was not seen in those with more advanced symptoms.[69] The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines do not support the use of an ICD if overall survival is estimated to be <1 year.[1] Because patients will often overestimate the benefit from an ICD,[70] it is important for clinicians to help them to understand their goals and to decide if an ICD is consistent with those goals. In patients with end-stage heart failure, depending on the individual preferences, it may (or may not) be appropriate to deactivate the ICD.[71]

Heart Transplantation

An estimated 6,300 heart transplantations are performed worldwide each year, with a median survival of 11 years and >90% reporting normal functional capacity.[72] These numbers have remained consistent over the past several years and affirm that heart transplantation is a viable and effective therapy for select patients with stage D heart failure. However, the therapy is limited by the availability of donor organs, so patient selection is critical.[73] Briefly, patients should have stage D features and either be inotrope dependent or have poor performance on cardiopulmonary exercise testing (CPET). Appropriate patients to list for heart transplant are those with a peak VO_2 on CPET of <10 mL kg^{-1} min^{-1} or <50% of predicted. Candidacy may be based on other clinical parameters for patients with a peak VO_2 of 10–14 mL kg^{-1} min^{-1}.

Mechanical Circulatory Support

MCS devices, such as percutaneous and durable ventricular assist devices (VADs) and total artificial hearts, have experienced a dramatic and exponential growth in utilization,[14] driven mostly by the availability of durable continuous-flow pumps, expected to last for several years, and improved survival statistics.[55] Clinical trial data suggest that anticipated survival with LVADs could be expected to be ~85% at 1 year with an average survival of ~3 years.[74–76] There have now been >24,000 continuous-flow VADs implanted.[77,78] The devices can be used as a bridge to transplantation to improve quality of life and survival in patients listed for transplantation, as destination or lifelong therapy (DT) in patients who do

not qualify for transplant, or for the occasional but real opportunity for explantation due to myocardial recovery. DT has expanded MCS to a large population of older patients and those with significant comorbidities that preclude cardiac transplantation.

A detailed discussion of patient selection for MCS can be found in the literature.[73,79,80] General principles include timely referral, lack of other treatment options, severity of illness that is high enough to warrant the risk, anticipation of good survival and outcome, and motivation to proceed with therapy. In patients with an estimated 1-year survival of ≤85%, MCS could be considered. The Heartmate II Risk Score (HMRS) is an attempt to help predict post-procedure outcomes,[81] but it should not replace clinical and surgical judgment, because patients with poor HMRS scores may have good outcomes.[82] Nonetheless, the medical and surgical team should agree that the operative risk is acceptable, and that the comorbid conditions will allow for a meaningful survival of ≥2−3 years.

Patient motivation is a critical factor in MCS success. Patients and their families must have enough of a desire to live to overcome the fear of surgery and potential adverse outcomes, and to learn how to live with portable equipment and batteries. This decision often takes time and is best done with the assistance of a palliative care team to help patients think through their options and life goals. Palliative care consultation before implantation has been associated with improved outcomes after implantation.[83] In the United States, coverage for DT is linked to having a palliative care specialist involved in the MCS program.[84]

Continuous Inotrope Infusion

Continuous inotrope infusions can be used at home to improve quality at the end of life. For patients who demonstrate a clear improvement in symptoms with inotrope therapy and fail attempts to wean, discharge to home has been associated with an initial good level of functioning;[6] however, median survival is poor (eg, 3.4 months, although the majority of these patients died at home and avoided repeated hospitalization).[6] In another small cohort (n = 20) of patients on the transplantation list, home inotrope infusions were associated with a 70% reduction of hospital days and thereby with substantial savings in the cost of care. Of the 20 patients, 13 received transplants or remained on the list and 7 died after clinical deterioration and removal from the transplantation list.[85] Both REMATCH and INTREPID have shown superiority of MCS over inotropic therapy in DT patients with stage D heart failure.[4,5]

Criteria for home inotrope intrusions are presented in Table 3. Guideline statements are clear that the use of intermittent or continuous inotrope infusions outside of these parameters are considered to be harmful and inappropriate.[1] In some limited circumstances, inotropes may be used as a bridge to decision to provide time to assess a patient's candidacy for MCS or other advanced therapies.

Impact of Age, Comorbidities, and Psychosocial Issues

Heart failure is strongly related to advanced age and noncardiac diseases. Therefore, heart failure seldom occurs in otherwise healthy young individuals, but when it does, consideration of advanced intervention (eg, MCS, transplantation) is usually appropriate. These associations between heart failure, age, and comorbidity tend to be exacerbated in advanced, stage D heart failure, where age and comorbidity can decrease the ability of the body to compensate for severe cardiac dysfunction and, simultaneously, severe cardiac dysfunction can exacerbate existing noncardiac (eg, renal, hepatic, pulmonary, cognitive, and psychosocial) issues.

Age

Heart failure is largely a disease of older people, and therefore definitions, evaluations, and treatment strategies for advanced heart failure should consider how increasing chronologic age influences the disease.[20,86−91] Apart from the obvious association of advancing age with other comorbidities, advanced age carries an independent association with progressive heart failure and adverse outcomes in nearly all prognostic models.[92]

Malnutrition, Frailty, and Sarcopenia

Aging is frequently accompanied by the comorbid conditions of frailty and malnutrition, which are important predictors of outcome with heart failure and affect the feasibility of advanced heart failure therapies. Frailty is the biologic syndrome reflecting impairment in multiple interrelated organ systems causing decreased homeostatic reserve and increased vulnerability to stress.[93] Although commonly assessed by the "eyeball test," frailty can be specifically defined by the presence of ≥3 of the following criteria: weight loss of >10 pounds in 1 year, physical exhaustion by self report, weakness as measured by grip strength, decline in walking speed, and low physical activity.[94] Sarcopenia, defined as having a lean body mass 2 standard deviations below the sex-specific mean in a young healthy sample, is central to the pathophysiology of frailty.[95] Cachexia, a related phenomenon, shares important features with frailty, such as fatigue, weakness, and sarcopenia; however, cachexia is characterized by weight loss and wasting.[96]

Measures of frailty, even after adjustment for underlying age and comorbidities, are highly predictive of death, incident disability, and hospitalization in patients with heart disease and those undergoing cardiac surgery.[97] Specific to the advanced heart failure population, a baseline measure of frailty before destination LVAD implantation was shown to provide incremental prognostic information. Compared with those who were not frail, patients who were intermediately frail (adjusted hazard ratio [HR] 1.70) and frail (adjusted HR 3.08) were at increased risk for death (P for trend = .004).[98]

Determining whether frailty, cachexia, and sarcopenia will improve with advanced therapies such as MCS or transplantation is a major challenge but ultimately can dictate the course of therapy.[99] Optimal measures of frailty and the ability to distinguish treatment-sensitive from treatment-resistant frailty remains an area of need.[99]

Psychosocial Issues

Heart failure commonly overlaps with psychosocial issues, and this overlap is accentuated with increasing heart failure severity. The prevalence of depression among heart failure patients is estimated to be 22%, but increases with worsening heart failure symptoms. Among NYHA functional class I patients, the prevalence of depression is 11%, whereas among NYHA functional class IV patients this rises to 42%.[100] Compared with heart failure patients without depression, depressed patients have decreased medication adherence, worse health status, increased health care utilization, and increased mortality. Depression therefore poses additional challenges to clinicians caring for complex patients with advanced heart failure.

Similarly, social instability complicates advanced heart failure. Risk models for adverse outcome in heart failure have variably identified income, disability status, Medicaid health insurance, unmarried status, living alone or at a distance from hospital care, and history of alcohol or drug abuse as independent predictors of worsening heart failure and adverse outcomes.[101] Cognitive impairment is also a predictor of mortality in heart failure and may affect a patient's self-care ability, thereby limiting therapies for stage D heart failure.[102]

Reconciling Survival Versus Quality of Life

Prognosis for those with advanced heart failure is often framed as an issue of death prevention and survival; however, that perspective discounts the relative importance that patients may place on quality rather than quantity of life.[103–105] Reconciliation of this issue is a major focus of funding agencies such as the Patient-Centered Outcome Research Institute, and efforts are increasingly being directed in the clinical arena toward delivery of care that is best aligned with patient preferences. Although attempts have been made to determine factors associated with the decision to choose quality of life over quantity (or vice versa), identification of a reliable set of predictor variables has remained elusive.[106] Complicating matters, the decision itself is static for some and dynamic for others, particularly between periods of symptomatic decompensation and recovery.[107,108]

Given the relative uncertainty and fluidity of advanced care decisions, it should come as no surprise that physicians are frequently inaccurate in their assessment of patient preferences for resuscitation.[107] This underscores the need for open-ended discussion with patients and their proxies aimed at soliciting insight into how they perceive their heart failure to be affecting them, along with specific wishes and goals for advanced care.[103,109]

Shared Decision Making

Guiding patients and their family members through the process of delineating an advanced care plan can be a daunting task. The optimal approach involves shared decision-making, where options for medical care are discussed with acknowledgment and legitimization of the complex trade-offs behind each choice.[103] Working to understand patients' values, especially the emphasis they place on nonmedical considerations, such as spirituality, interpersonal relationships, and familial or societal obligations, can help ensure that decisions remain true to individual preferences. Although survival and symptom burden are the typical points of emphasis, functional limitations, loss of independence, and overall quality of life should be addressed, as well as the potential for development of and recovery from major adverse events. Involving palliative care specialists can facilitate the conversation and, for patients who prioritize comfort over longevity, help to ensure access to necessary resources for enactment of a less aggressive care path.[110]

Ideally, such conversations should be initiated before the transition to terminal stages of advanced heart failure, when the patient is most capable of providing meaningful feedback and comprehending the information being presented. However, onset of clinically relevant milestones, such as a loss of ability to carry out activities of daily living despite adequate treatment or a failure to respond to escalating medication doses, can influence patient perspectives and should serve as a trigger for reappraisal of an established advanced care plan.[103] Thus, rather than a singular decision, this should be seen as an iterative process that evolves with the patient's disease state.

Balancing the Scorecard

For many, the expected clinical trajectory is an important factor that guides their decision making. Making matters challenging, patients tend to overestimate their likelihood of survival compared with criterion-based prediction models.[111] Although informing patients of their anticipated prognosis is an important part of the conversation, such predictions are not an exact science, and reinforcing this uncertainty can help to calibrate survival expectations.[103,104] However, value systems differ, and objectively determining the relative emphasis a patient or family members place on quality versus quantity of life is also needed, particularly for decisions related to life-preserving treatment options.

Used primarily to establish utility values for quality-adjusted life-year assessment in research,[112] time trade-off (TTO) analysis may be translatable to clinical practice, allowing patients to consider precisely how much time alive they are willing to sacrifice in return for living symptom or event free.[113] Although studies have shown that most patients with advanced heart failure are "zero traders," meaning that they are not willing to sacrifice any time alive, a sizeable proportion would elect to forego at least some time to feel better.[106,108]

The value of TTO lies in its ability to gauge the balance between quality and quantity of life, but the insight it provides is distinct from actual resuscitative preferences. Studies have shown that, even among zero traders, not all want cardiopulmonary resuscitation.[106,108]

Hospice Care in Heart Failure

Hospice care is specialized medical care for patients with life-threatening illnesses focused on symptom relief and improving quality of life for patients and their families and caregivers. The focus is traditionally on relief of pain and other distress, but also on easing psychologic, social, spiritual, and existential suffering.

The ACCF/AHA 2013 Guideline for the Management of Heart Failure states that "palliative and supportive care is effective for patients with symptomatic heart failure to improve quality of life."[1] The Heart Failure Society of America (HFSA) guideline goes further, with multiple recommendations about palliative care, including guidelines regarding necessary education of patients about quality of life, prognosis, risk of death (including sudden cardiac death) despite ongoing active treatment, goals and efficacy of therapeutic plans, and discussions of hospice or end-of-life care and wishes, including explicit discussion of defibrillator deactivation.[114] In addition, the HFSA guideline stresses the importance of reassessment of care goals and end-of-life strategies at key clinical turning points.[114] Most recommendations in the HFSA guideline are a strength of evidence C,[114] reflecting the absence of significant high-quality studies on these topics, particularly in the heart failure literature.

Despite the clear consensus among experts, only 34% of heart failure patients are referred to some type of palliative care in the last 3 months of life. Those not referred receive fewer therapies aimed at comfort, particularly before the last week of life.[115] The mean time from referral to death in heart failure patients moved into palliative medicine programs is <2 weeks.[115]

The HFSA has recently produced a white paper on end-of-life care that discusses the role and use of palliative and hospice services in detail.[109] Similarly, the Heart Failure Association of the European Society of Cardiology has written a position statement addressing use of palliative and hospice care in heart failure.[116] Interested readers are referred to these papers[109,116] for in-depth discussion of all issues surrounding palliative care in stage D heart failure. The Palliative Care in Heart Failure (PAL-HF) study, sponsored by the National Institute for Nursing Research, aims to assess the impact of an interdisciplinary palliative care intervention combined with usual heart failure management on health-related quality of life (clinicaltrials.gov NCT01589601).

Myocardial Recovery From stage D

In some patients with stage D heart failure, MCS devices may provide an opportunity for "bridge to recovery." Owing to the hemodynamic stability and clinical improvements in patients receiving MCS, such devices can also serve as a platform for novel pharmacologic or biologic therapies that might aid in this process. Early clinical anecdotes of "spontaneous" recovery of LV function in patients receiving MCS introduced the contemporary concept that severe LV dysfunction and advanced heart failure could be at least temporarily reversed with significant mechanical unloading of the left ventricle. The clinical occurrence of MCS-facilitated myocardial recovery varies widely in published reports, but it probably occurs in 5%−10% in most centers.[117] In a highly publicized report from the United Kingdom, 11/15 patients (73%) experienced enough myocardial recovery to justify LVAD explantation, and 89% were free of heart failure after 4 years.[118] In contrast, only 22/271 patients (8%) from a variety of centers experienced sufficient recovery for device explantation.[119] In the most recent Interagency Registry for Mechanically Assisted Circulatory Support report, the rate of recovery at 1 year in bridge-to-transplantation continuous-flow LVADs was only 1%.[55] The heterogeneity of these reports is explained in large part by differences in patients, clinical practices, and definitions. Differences in concomitant medical therapy, implanted devices, underlying etiologies (eg, ischemic versus nonischemic), and definitions of recovery are compounded by variable durations of pre-implantation disease and MCS support, degrees of hemodynamic unloading, and explantation criteria. Despite the relatively uncommon (but not rare) occurrence of myocardial recovery, many centers routinely maximize heart failure medications after implantation and regularly assess myocardial recovery with weaning or "turn-down" protocols to optimize the chances of recovery.

Despite the clinically vague distinction between myocardial remission and recovery, improvements in myocardial biology, structure, and function have all been documented. Perhaps the most straightforward sign of myocardial recovery is the echocardiographic appearance of the supported LV. In a prospective series of 80 MCS patients studied with the use of serial echocardiography, ejection fraction improved to $>40\%$ in 19%, and one-third experienced a relative increase in EF of $\geq 50\%$.[120] Both LV dimensions and LV mass significantly decreased over time. Moreover, improvements were seen as early as 30 days after implantation, were maximal after 6 months, and were sustained at 1 year. Importantly, atrophy (eg, decreases in LV size and mass to below normal ranges) was not seen despite concerns noted in nonhuman models of chronic MCS support. These improvements in structure and function have paralleled improvements in the neurohormonal milieu,[121−123] although it is important to note that the magnitude of these improvements have not been sufficient to normalize their values, nor are they uniformly reflected at the tissue level. Reassuringly, improvements in cardiac sympathetic innervation[124] and beta-adrenergic signaling[125,126] have been documented. Endothelial and microvascular function also appear to improve.[127−133]

Despite the enthusiasm for myocardial recovery, it remains an elusive therapeutic end point for most patients. Significant questions remain, including identifying the specific etiology causing the primary cardiomyopathy, the definition of myocardial recovery versus remission,[134] the delineation of molecular, structural, and biologic signatures of this end point, duration and nature of support, and need for and nature of specific adjuvant therapies (eg, stem cells, growth factors, gene therapies). Even the optimal type of mechanical hemodynamic unloading remains uncertain, because pulsatile, continuous, and counterpulsation devices now exist. Uniform criteria for device explantation have not been determined, and critical questions, such as the need for assessing inotropic reserve, have not been settled.

Despite these unresolved issues, clinical "proof-of-principle" trials have been attempted (eg, Harefield Recovery Protocol Study [HARPS]) or are in progress (eg, Remission From Stage D Heart Failure [RESTAGE-HF].

Costs of Care

Heart failure has long been recognized as a disease state with significant costs.[88] It is therefore not unexpected that on a per-patient basis, stage D heart failure patients have extremely high costs. The higher resource utilization and cost in the last year of life has been noted in heart failure patients both in clinical trials and in administrative datasets,[135,136] and varies by mode of death. Patients who die suddenly have lower associated health care costs versus those who die because of heart failure. These higher costs are associated with a significant increase in use of health care resources, including hospitalizations and provider visits.

The traditional cost-effectiveness ratio benchmarks used to identify an intervention as economically attractive is $50,000 per life-year added; the benchmark for identifying an intervention as not economically attractive is $100,000 per life-year added. These benchmarks should be viewed only as guideposts and not as national standards. Within the United States, different purchasers may identify their own benchmarks when deciding if the additional cost of an intervention provides a significantly large clinical benefit.

A significant amount of work regarding cost-effectiveness in stage D patients has focused on cardiac transplantation and MCS, owing to the marked benefit in survival for appropriately selected patients that is achieved at very high cost. Overall mortality rates of transplantation remain relatively low, and the procedure provides a significant clinical benefit in terms of survival and quality of life. Although MCS mortality is higher, likely due to the broader patient population selected for DT, overall mortality has decreased significantly over the past few years owing to improved technology, better patient management, and improved care process.

The costs for transplantation and MCS have increased over time. From 2005 to 2009, the mean annual cost of transplantation increased by 40% from $120,413 to $168,576, and that of MCS increased by 17% from $177,508 to $208,522.[137] Similar annual costs for MCS implantation have been identified in the Medicare beneficiary population.[138] The cost of continuous-flow MCS as destination therapy has been identified as being $198,184 per quality-adjusted life-year (QALY) and $167,208 per life-year gained.[139] This cost is significantly better than the $802,674 per QALY identified for pulsatile LVADs, the first-generation devices.[140] Although there has been no recent analysis of cost-effectiveness of transplantation in the United States, the estimate of cost per life-year gained for heart transplant patients in the Netherlands has been projected to be $38,000.[141] For comparison, CRT has been associated with a favorable cost-effectiveness of $43,000 per QALY for CRT-defibrillator and $19,600 per QALY for CRT-pacemaker.[142]

Future Directions

The uncertainty as to which patients benefit from invasive technologies, coupled with economic constraints of the current health care system, have elevated the issue of appropriate patient selection to the forefront of research and policy. Existing prognostic models for advanced heart failure and the prediction of adverse outcomes following advanced therapies remain suboptimal.[81,92] Despite the recognition of older age, multimorbidity, and frailty as important elements in risk prediction and medical decision making for patients with advanced heart failure, the measurement and adoption of frailty measures in routine clinical practice remains a critically unmet need. Improved and simplified assessments of frailty are instrumental to refining estimates of risk and guiding patients toward personalized treatment plans that will maximize their likelihood of a good outcome. Moreover, the likelihood of the reversibility of frailty and end-organ dysfunction in advanced heart failure remains largely unknown and requires greater study.

The next few years will see continued efforts to better our understanding and management of stage D heart failure. Because of the heterogeneity of individual patient trajectories, refinements in quantifying morbidity and mortality risk are urgently needed to help guide appropriate-use criteria and match intensive and costly resource utilization to those patients most likely to benefit. An important challenge will be to design appropriate clinical trials that test new advances in MCS without subjecting patients and investigators to redundant regulatory and administrative processes.[143] For now, durability, infection, pump thrombosis, stroke, and hemorrhage remain significant barriers to greater adoption of this technology. It will be important to understand the place of MCS in juxtaposition to the traditional definitive therapy of heart transplant as MCS approaches the ultimate goal of "forgettable" circulatory support.[144,145]

Rapid technologic improvements in MCS will also drive new concepts in myocardial recovery and change the paradigm that advanced heart failure is irreversible. But many questions remain, including who should be considered for myocardial recovery. Clarifying molecular, structural, or functional signatures of recovery are currently being explored, and those studies will yield both clinically practical information to guide explantation and new molecular and protein targets for therapy. Should hemodynamic unloading be attempted earlier in the heart failure course? Moreover, what is the optimal hemodynamic unloading strategy, eg, continuous, pulsatile, or counterpulsation? What should be the duration of support? What adjuvant therapies can use MCS as a platform? The role of partial LV support is also a subject of investigation.[146]

Finally, the balancing of cost, clinical benefit, and risk will continue to be emphasized in the coming years. The improvements in quality of life on MCS will need to be quantified and assessed in the context of immediate and lifetime costs. Moreover, with greater emphasis on population health by care providers and insurers, the role of sophisticated, advanced, and expensive technologies will be challenged.

Conclusion

Advanced (stage D) heart failure presents a complex set of challenges for many stakeholders, including patients and their families, clinicians, health care systems, researchers, pharmaceutical and device industries, and regulators. The many uncertainties and unmet needs described in this paper have created an environment where the care of stage D patients is frequently based on only a modest body of scientific evidence and therefore, in many cases, relies on the personal experiences of individual physicians. Although reconciling survival versus quality of life and setting realistic expectations are common dilemmas, many effective interventions can still be offered to patients. These options range from the optimization of medical and device therapy to MCS or cardiac transplantation to palliative or hospice care. The field is rapidly evolving, and advances in technology have the potential to continue to improve the outcomes of these often desperate patients. We think that the HFSA has a unique opportunity and obligation to lead this important field through quality research, collaborative initiatives, and development of rigorous standards to guide treatment decisions.

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