

MINI-FOCUS ISSUE: ADVANCED HEART FAILURE

STATE-OF-THE-ART REVIEW

Advanced Heart Failure

Epidemiology, Diagnosis, and Therapeutic Approaches



Lauren K. Truby, MD, Joseph G. Rogers, MD

HIGHLIGHTS

- The prevalence of heart failure is increasing as the population ages. As a result of advances in medical therapy for heart failure, more patients are living longer and with more end-stage disease.
- The current review focuses on the diagnosis and management of advanced heart failure, including cardiogenic shock, temporary mechanical circulatory support, durable heart failure therapies including left ventricular assist devices and heart transplantation, and palliative care.
- Future directions discussed include translational research efforts in myocardial recovery, emerging left ventricular assist device technology, and innovative approaches to post-heart transplant care.

ABSTRACT

In broad terms, “advanced” heart failure describes a clinical syndrome characterized by persistent or progressive symptoms and ventricular dysfunction despite guideline-directed medical therapy. Clinically the definition is often dependent upon iterative and integrated clinical assessments to identify patients with worsening status and reliance on specific therapies. This review examines current consensus definitions, highlights strategies for risk stratification and prognostication, and examines short- and long-term treatment strategies. Lastly, this paper explores future directions of research and development for the field. (J Am Coll Cardiol HF 2020;8:523-36) © 2020 by the American College of Cardiology Foundation.

EPIDEMIOLOGY OF ADVANCED HEART FAILURE

Heart failure (HF) affects 6.2 million American adults, with an incidence approaching 21 per 1,000 population after the age of 65 years (1). Projections estimate that by 2030, more than 8 million people over the age

of 18 years will be affected by HF (2,3). Estimating the prevalence of advanced HF remains an epidemiological challenge as a result of the relatively low incidence of the condition and the dependence of the definition on an evolving series of therapies. Over a decade ago, a population-based, cross-sectional analysis of Olmstead County, Minnesota, suggested

From the Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose. John Teerlink, MD, was Guest Editor on this paper.

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ABBREVIATIONS AND ACRONYMS

CAV = cardiac allograft
vasculopathy

CS = cardiogenic shock

DCD = donation after
circulatory death

DT = destination therapy

HF = heart failure

INTERMACS = Interagency
Registry for Mechanically
Assisted Circulation

ISHLT = International Society
for Heart and Lung Transplant

LV = left ventricular

LVAD = left ventricular assist
device

NYHA = New York Heart
Association

PGD = primary graft
dysfunction

RV = right ventricular

VA-ECMO = venoarterial
extracorporeal membrane
oxygenation

advanced HF affected 0.2% of the population ($n = \sim 13,000$), whereas data from the ADHERE (Acute Decompensated Heart Failure) national registry suggested a prevalence of closer to 5% among hospitalized patients ($n = \sim 23,000$) (4,5). With the global burden of HF increasing, however, advanced disease will undoubtedly increase in tandem. Last year alone, more than 3,000 patients were treated with a left ventricular assist device (LVAD), and more than 3,000 patients received heart transplants in the United States, with an additional 3,500 patients awaiting transplantation (6,7).

DEFINING ADVANCED HF

Multiple classification systems have been developed to characterize patients with HF and define those with advanced disease (Central Illustration). For example, New York Heart Association (NYHA) functional class IV defines those with symptoms at rest and with any physical activity. In 2001, the American College of Cardiology and the

American Heart Association developed a new construct for defining HF, describing Stage D patients as those who require specialized interventions due to refractory symptoms despite maximal medical therapy (8). The Interagency Registry for Mechanically Assisted Circulation (INTERMACS) classification system was developed to risk stratify patients with advanced HF to better define prognosis and urgency of intervention (9). These 3 classification systems may be used in parallel in order to more precisely define where an individual patient lies on the spectrum of this progressive disease. Professional societies have also published consensus definitions to improve the early identification and treatment of patients that rely on combinations of symptoms, objective data, and therapeutic interventions (Figure 1) (10, Supplemental Refs. 11,12).

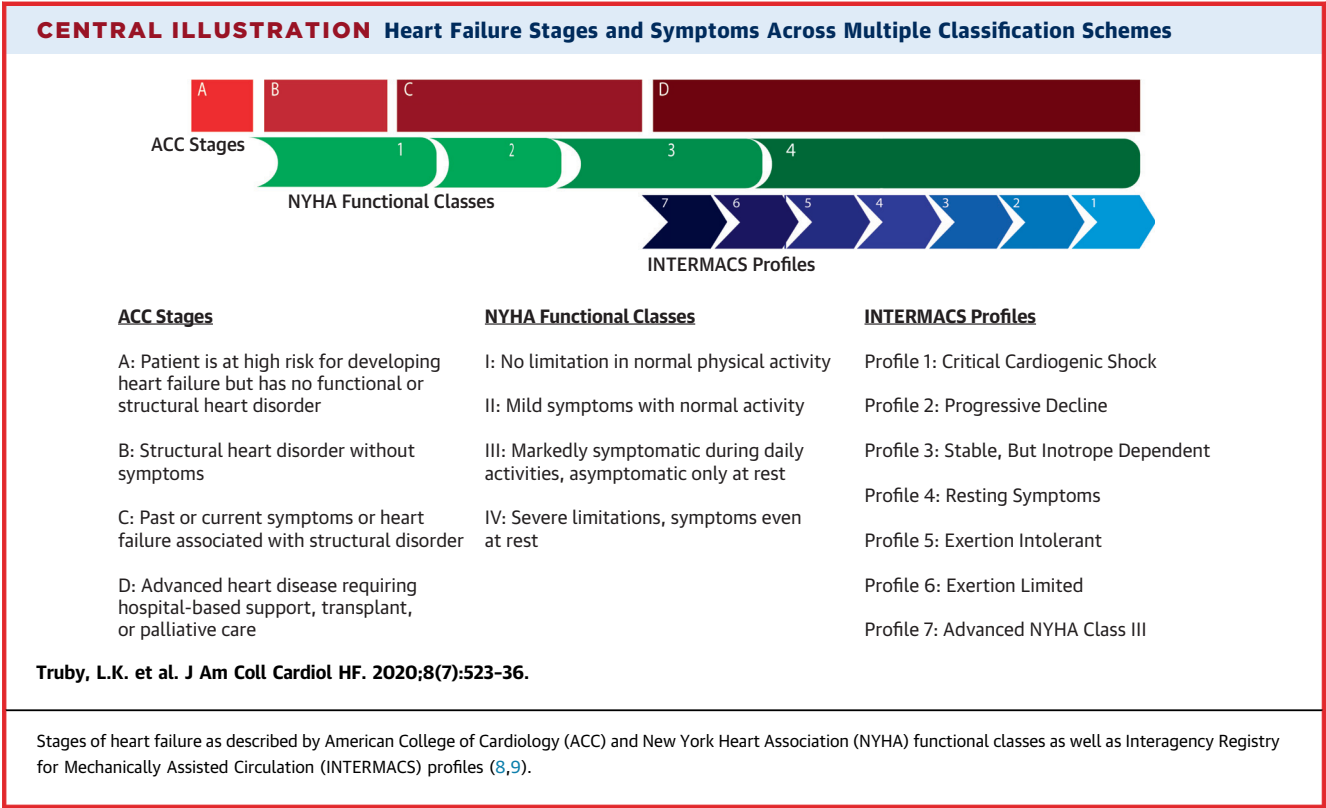
The highly unpredictable clinical course of HF can challenge even the most experienced clinician to correctly identify the optimal timing of referral to a HF specialist. Whereas some HF cases are abrupt and obvious, others are related to progressive diseases that evolve subtly over time. The addition of objective measures of exercise performance, quality of life, cardiac structure and function, biomarkers and laboratory assessments, and arrhythmia burden are useful in the ongoing evaluation of patients with chronic HF and may serve as important adjuncts to obviate the sense of clinical stability. One particularly helpful

mnemonic that may help identify patients in need of referral to a HF specialist is “INEEDHELP,” which integrates clinical history, hospitalizations, medication intolerance, in addition to symptoms and end-organ dysfunction (Supplemental Figure 1) (Supplemental Refs. 13,14). Consensus supports the concept of early referral to avoid the debilitation and end-organ dysfunction that accompanies prolonged advanced HF and may preclude candidacy for advanced therapies (Figure 2) (Supplemental Refs. 11,15,16).

CLINICAL APPROACH TO THE PATIENT WITH ADVANCED CHRONIC HF

Patients should have a thorough evaluation to exclude reversible causes of HF and ensure treatment with maximally tolerated guideline-directed medical therapy (8). Testing for ischemia in selected patients, surgical or percutaneous management of valvular disease, treatment of atrial and ventricular arrhythmias (including high premature ventricular contraction burden), evaluation for other systemic conditions such as thyroid disease and sarcoidosis, and a trial of abstinence from substance abuse may identify patients whose native cardiac function will sufficiently improve. In addition to renin-angiotensin antagonists, beta-blockers, and aldosterone antagonists, angiotensin receptor-neprilysin inhibitors are now routinely recommended in patients with chronic NYHA functional class II/III HF symptoms and adequate blood pressure, although their efficacy and safety have not yet been evaluated in patients with advanced HF (Supplemental Ref. 17). Cardiac resynchronization therapy can also improve symptoms, exercise capacity, reverse remodeling, and ejection fraction in appropriately selected patients (Supplemental Ref. 18). For those with moderate-to-severe secondary mitral regurgitation, transcatheter mitral valve repair appears to improve survival and freedom from HF hospitalizations (Supplemental Ref. 19). Consideration of candidacy for advanced HF therapies is appropriate for those with residual ventricular dysfunction and limiting symptoms despite aggressive attempts at medical, electric, and mechanical optimization. In the absence of obvious contraindications to advanced therapies, the patient should undergo assessment of clinical and hemodynamic stability, systemic perfusion, and end-organ function. Evidence of shock or rapidly progressive renal/hepatic dysfunction should prompt urgent referral to a specialized HF center (Figure 3).

Cardiopulmonary exercise testing may be the singular most important risk stratification test in patients with advanced HF (Supplemental Ref. 20). The



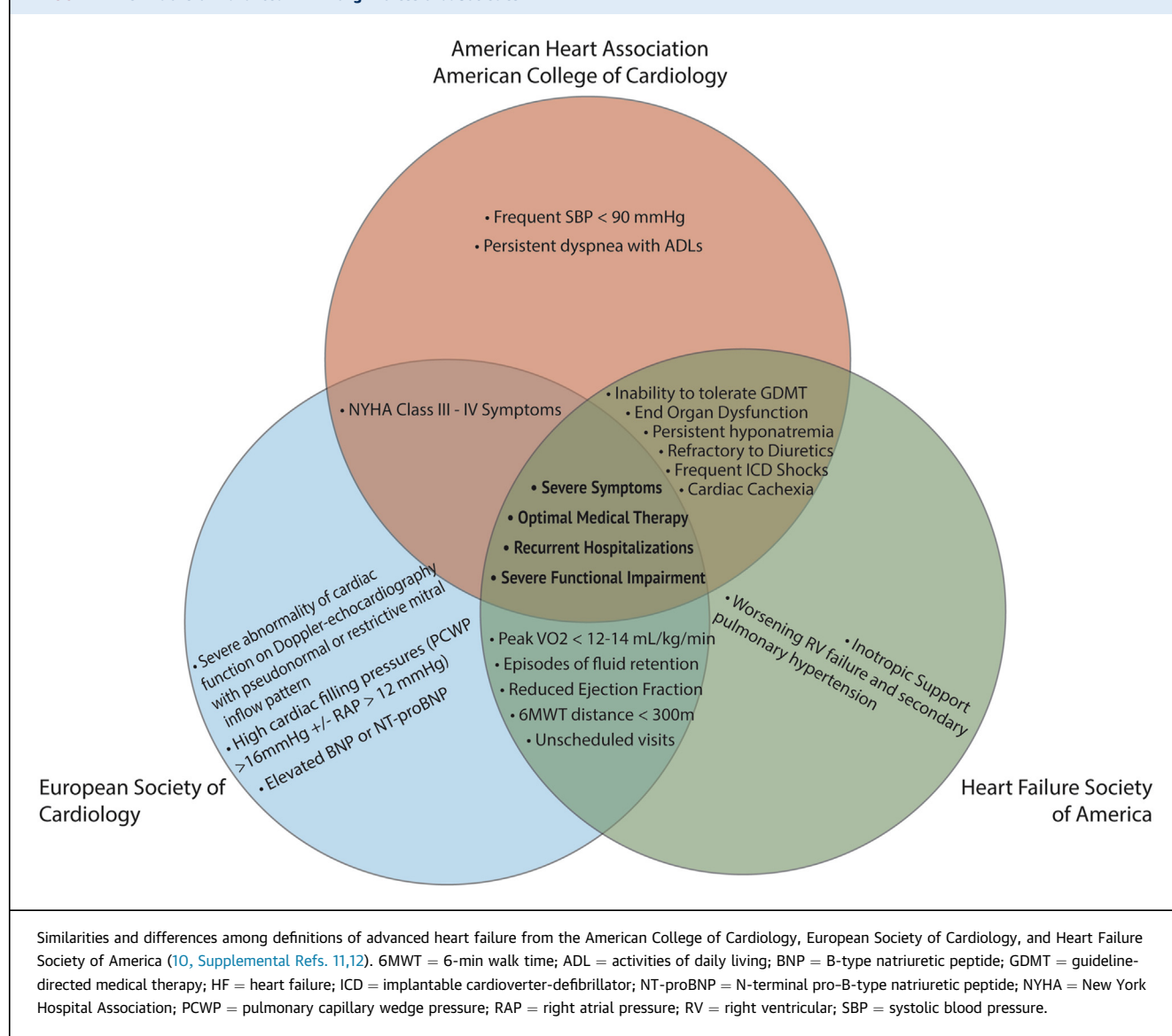
International Society for Heart and Lung Transplant (ISHLT) guidelines support transplant evaluation in those with a peak $\text{VO}_2 < 12 \text{ ml/kg/min}$ (or $< 14 \text{ ml/kg/min}$ if beta-blocker intolerant) or $< 50\%$ predicted value (Supplemental Refs. 21,22). In addition to peak VO_2 , patients with a ventilatory equivalent of carbon dioxide (V_E/VCO_2) > 35 have a poor prognosis and should be considered for advanced therapies (Supplemental Ref. 22). Another commonly used metric is the 6-min walk distance: a measure of functional capacity reflective of exercise performance and the patient's ability to perform the activities of daily living. The distance walked in 6 min is highly correlated with peak VO_2 and its impact on survival (Supplemental Refs. 23,24).

Right heart catheterization is a critical component of the assessment and management of patients in cardiogenic shock (CS) and patients being evaluated for advanced therapies (Supplemental Refs. 25,26). Invasive hemodynamics can be particularly useful to inform decision-making regarding specific pharmacotherapy and subsequent durable advanced heart failure therapies by providing the clinician assessment of left- and right-sided cardiac filling pressure, presence of pulmonary hypertension, cardiac output,

and measures of right ventricular (RV) performance (Supplemental Refs. 27,28). The ability to optimize filling pressures has been shown to be a powerful predictor of outcomes—even to a greater degree than cardiac output alone (Supplemental Ref. 29). In a randomized, controlled trial of an implantable, ambulatory pulmonary artery pressure monitoring device that guided directed medical therapy in patients with NYHA functional class III HF, patients treated with hemodynamic monitoring experienced a significant reduction in hospitalization for decompensated HF (hazard ratio: 0.72; $p = 0.002$, number needed to treat = 8) (Supplemental Ref. 30). Patients in the treatment arm also had significantly lower pulmonary artery pressures, more days outside the hospital, and improvements in quality of life as compared with controls (Supplemental Ref. 31).

RV failure is common in advanced HF and is associated with increased mortality (Supplemental Ref. 32). In particular, RV dysfunction associated with pulmonary hypertension carries a poor prognosis (Supplemental Ref. 33). For those being considered for durable LVAD, pre-implantation RV dysfunction may represent a relative or absolute contraindication, because early post-operative RV

FIGURE 1 Definitions of Advanced HF Among Professional Societies



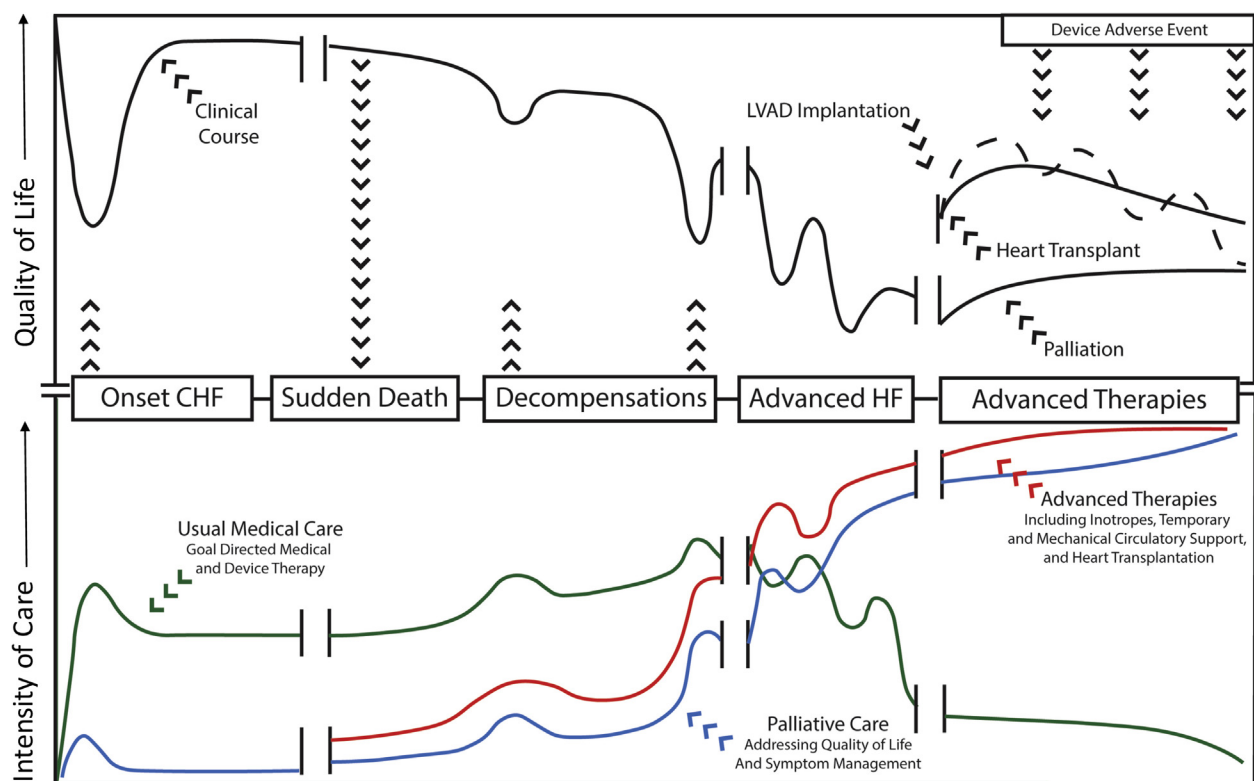
failure is associated with excessive morbidity and mortality (Supplemental Ref. 34). Optimization of right-sided filling pressures and RV performance is of paramount importance to successful LVAD outcomes. Pulmonary hypertension also represents a possible barrier to cardiac transplantation, with a pulmonary vascular resistance of >3 to 4 Woods units being associated with increased risk of post-transplant mortality (Supplemental Ref. 35). If prohibitive pulmonary hypertension is present, LVAD treatment as bridge to heart transplantation, in combination with pulmonary vasodilators, may normalize medically refractory pulmonary hypertension and

appears to have acceptable post-transplant outcomes (Supplemental Ref. 36).

SHORT-TERM THERAPY FOR CS AND DECOMPENSATED HF

Although disease-modifying medical therapies continue to be the cornerstone of HF treatment, patients with advanced disease and CS may require intravenous or mechanical therapies to stabilize clinical condition and end-organ function. Advanced therapies employed in these cases include vasoactive medication such as inotropes, intravenous

FIGURE 2 Clinical Course of Advanced HF

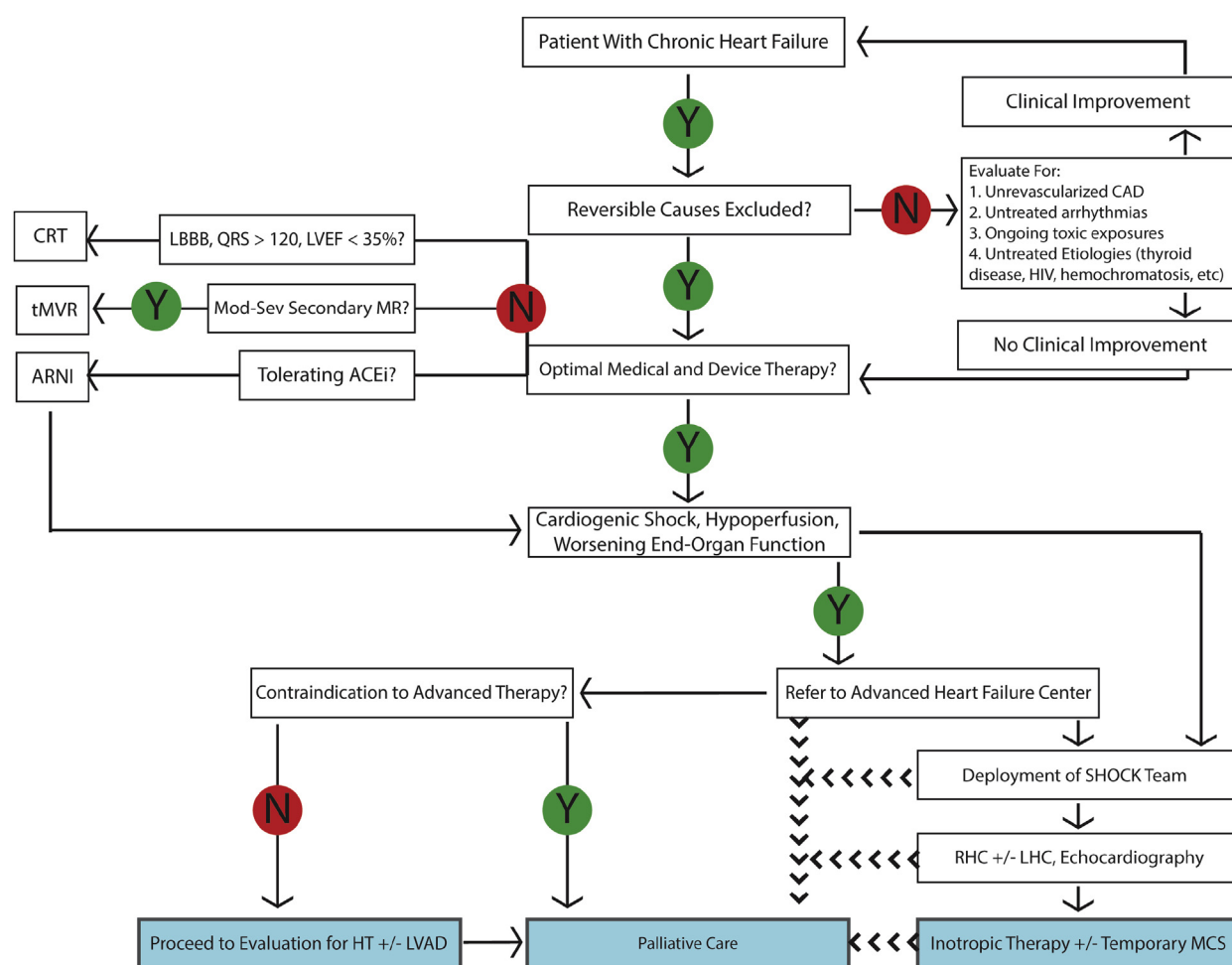


Expected natural history of the course of advanced heart failure (HF) including advanced therapies and palliative care interventions. The usual medical care and palliative care curves were adapted with permission from American Thoracic Society. Figure adapted with permission from Allen et al. (Supplemental Ref. 16). LVAD = left ventricular assist device.

vasodilators, vasopressors, and temporary mechanical circulatory support. Decision making surrounding choice and timing of these therapies often depends on resources available at a given center, patient candidacy for durable support or transplantation, center experience, and patient preference. There has been a recent paradigm shift in the care of patients with CS, with an emphasis being placed on early and aggressive treatment. In an effort to streamline the rapid deployment of the complex medical and surgical care these patients require, many centers have created multidisciplinary “shock teams” to standardize approaches to care in this patient population (Supplemental Refs. 37,38). The Society for Cardiovascular Angiography and Interventions recently issued a consensus statement that outlines 5 stages of CS varying from Stage A (“at risk”) to Stage E (“extremis”) as a tool to aid in the timely diagnosis and management of critically ill patients and to facilitate a common language for physicians and surgeons (Figure 4) (Supplemental Ref. 39).

Inotropic therapy and intravenous vasodilators, are mainstays of improving hemodynamics in decompensated HF, and have been studied extensively in clinical trials. Although routine use of inotropes is not recommended, experts agree that inotropic therapy is appropriate and beneficial in select patients with evidence of end-organ dysfunction and as a bridge to advanced therapies (Supplemental Refs. 11,40-43). However, in many patients, medical therapy alone is insufficient to optimize hemodynamics and improve end-organ function. A key role of the “shock team” is to identify the appropriate patients and timing of escalation of support (Figure 5). In these cases, temporary mechanical circulatory support devices may play a role as a bridge to recovery, bridge to decision, or bridge to heart replacement therapy (Supplemental Ref. 44). The specific device chosen largely depends upon the etiology of CS, the patient’s unique physiology, and the cardiac output augmentation required (Figure 6).

FIGURE 3 Diagnostic and Therapeutic Approach to the Patient With Advanced HF



For patients with chronic heart failure, initial investigation should involve identifying and treating reversible causes of cardiomyopathy. Once these have been excluded, or there has been no clinical improvement despite correction of these processes, guideline-directed medical therapy and device therapy should be optimized. Should worsening end-organ function or shock develop, patients should be transferred to a specialized center and evaluated for advanced therapies (Supplemental Ref. 13,15,17-19). Palliative care should be involved with all patients ill enough to qualify for advanced therapies whether or not they are a candidate for ventricular assist device or transplant. ACEi = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CAD = coronary artery disease; CRT = cardiac resynchronization therapy; HIV = human immunodeficiency virus; HT = heart transplantation; LBBB = left bundle branch block; LHC = left heart catheterization; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; MR = mitral regurgitation; RHC = right heart catheterization; tMVR = transcatheter mitral valve replacement.

The intra-aortic balloon pump is a percutaneously deployed catheter-based balloon that inflates during diastole and deflates during systole, augmenting coronary perfusion and myocardial oxygen supply while reducing left ventricular afterload (Supplemental Ref. 45). Although its overall contribution to cardiac output is modest, case series and cohort studies suggest benefit in a broad range of clinical conditions including myocardial infarction, post-cardiotomy shock, and decompensated chronic HF. As a result, it

continues to be a mainstay of therapy in CS (Supplemental Refs. 46-49). Novel technology and surgical approaches have facilitated expansion of axillary insertion techniques both in hospitalized patients and in the ambulatory setting as a bridge to heart transplantation (Supplemental Refs. 50,51).

The use of catheter-based ventricular assist devices has rapidly expanded as a therapeutic modality in refractory CS. The Impella microaxial flow device (Abiomed, Danvers, Massachusetts) can be

FIGURE 4 SCAI Classification of CS

		Physical Exam	Laboratory Values	Hemodynamics
E Extremis	A patient that is experiencing circulatory collapse with ongoing CPR or with ongoing clinical instability despite being supported by multiple interventions	- Near Pulselessness - Cardiac Collapse - Defibrillation - Mechanical Ventilation	- pH < 7.2 - Lactate > 5	- No SBP w/out resuscitation - Ongoing shock despite maximal support
D Deteriorating	A Category C patient who has failed to improve despite initial interventions.	- Looks unwell - Hypervolemic - Cold, Clammy - Low UOP - AMS	- Doubling or Cr or > 50% rise in Cr - Abnormal LFTs - Elevated BNP - Lactate > 2	- CI < 2.2 - PCWP > 15 - CVP/PCWP > 0.8 - PAPI < 1.85 - CPO < 0.6
C Classic	A patient that develops hypoperfusion requiring intervention (inotropes, vasopressors, mechanical circulatory support).	- Looks unwell - Hypervolemic - Cold, Clammy - Low UOP - AMS	- Doubling or Cr or > 50% rise in Cr - Abnormal LFTs - Elevated BNP - Lactate > 2	- CI < 2.2 - PCWP > 15 - CVP/PCWP > 0.8 - PAPI < 1.85 - CPO < 0.6
B Beginning	A patient who has clinical evidence of relative hypotension and/or tachycardia without evidence of hypoperfusion	- Elevated JVP - Rales in lungs - Warm and well perfused - Normal mentation	- Minimal renal dysfunction - Elevated BNP - Normal Lactate	- SBP < 90 or MAP < 60 or SBP < 30 mmHg below baseline - HR > 100 - CI > 2.2, PA Sat > 65
A At Risk	A patient who is not currently experiencing signs or symptoms of CS, but is at risk.	- Normal JVP - Warm and well perfused - Strong pulses - Normal mentation	- Normal end organ function - Normal Lactate	- CI > 2.5 L/min/m ² - CVP < 10 - PA Sat > 65%

Society for Cardiovascular Angiography and Interventions (SCAI) classification of cardiogenic shock with associated exam findings, laboratory values, and hemodynamics for each stage. Adapted with permission from Catheterization and Cardiovascular Interventions (Supplemental Ref. 39). AMS = altered mental status; CI = cardiac index; CPO = cardiac power output; CPR = cardiopulmonary resuscitation; CS = cardiogenic shock; CVP = central venous pressure; HR = heart rate; JVP = jugular venous pressure; LFT = liver function test; MAP = mean arterial pressure; PAPI = pulmonary artery pulsatility index; PA Sat = pulmonary artery oxygen saturation; UOP = urinary output; other abbreviations as in Figure 1.

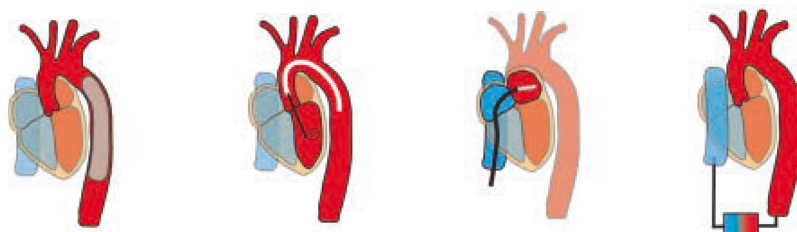
placed percutaneously via arterial vascular access across the aortic valve, where it draws blood from the left ventricular (LV) and ejects into the ascending aorta. In doing so, the device decreases LV preload and myocardial wall stress, reduces myocardial oxygen demand, and increases cardiac output and coronary perfusion. Small, randomized control trials comparing Impella 2.5 to intra-aortic balloon pump support have failed to demonstrate a survival benefit despite a more favorable hemodynamic profile (Supplemental Refs. 52,53). As a result, most clinicians use the Impella CP or Impella 5.0 for patients requiring greater hemodynamic support such as those with CS (Supplemental Ref. 44). Complications related to Impella include hemolysis and migration of the cannula resulting in damage to the mitral or aortic valve.

TandemHeart (LivaNova, London, United Kingdom) consists of an inflow cannula inserted in the femoral vein with access to the left atrium via trans-septal puncture, an extracorporeal centrifugal flow pump, and an arterial outflow cannula inserted into the femoral artery. In this configuration,

TandemHeart directly unloads the LV and provides a cardiac output up to 4 l/min. Due to the technical expertise required to position the device, it cannot be easily deployed at the bedside and carries increased risk of complications relating to cannula migration. Similar to other percutaneous devices, randomized controlled trials have yet to demonstrate a survival benefit (Supplemental Ref. 54).

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is capable of providing full cardiopulmonary support and has been increasingly used in refractory CS as bridge to heart replacement therapy, bridge to decision, or bridge to recovery (Supplemental Ref. 55). The general concept underlying VA-ECMO is that venous blood is drained from the right heart, passed through an oxygenator, and returned to the arterial circulation. In this way, both the circulatory and respiratory systems are supported. The 2 most commonly used cannulation strategies are: 1) peripheral cannulation in which a femoral venous cannula is advanced into the right atrium for drainage and a second cannula is inserted in the femoral artery; and 2) central cannulation in

FIGURE 5 Temporary Mechanical Circulatory Support



	IABP	Impella 2.5/CP/5	Tandemheart	VA-ECMO
Augmentation of CO (L/min)	0.5- 1.0	2.5 / 3.0 - 4.0/ 5.0	4.0 – 5.0	4.0 – 10.0
Hemodynamic Effects	▼ Preload	▼ Preload	▼ Preload	▼ Preload
	▼ Afterload	▲ Afterload	▲ Afterload	▲ Afterload
	▲ Stroke Volume	▼ Stroke Volume	▼ Stroke Volume	▼ Stroke Volume
	▲ Coronary Flow	-- Coronary Flow	-- Coronary Flow	-- Coronary Flow
	▼ PCWP	▼ PCWP	▼ PCWP	▼ PCWP
	▼ LVEDP	▼ LVEDP	▼ LVEDP	▲ LVEDP
Advantages	<ul style="list-style-type: none"> • Bedside insertion • Not anticoagulation dependent 	<ul style="list-style-type: none"> • Direct ventricular decompression 	<ul style="list-style-type: none"> • Addition of pulmonary support possible 	<ul style="list-style-type: none"> • Rapid bedside insertion • Pulmonary support
Disadvantages	<ul style="list-style-type: none"> • Minimal RV support • Immobilization 	<ul style="list-style-type: none"> • Imaging-dependent insertion • Hemolysis • Obligatory anticoagulation 	<ul style="list-style-type: none"> • Imaging-dependent insertion • Immobilization 	<ul style="list-style-type: none"> • Incomplete LV decompression • Need for perfusion support
Contraindications	<ul style="list-style-type: none"> • Severe PAD • AAA • Significant AI 	<ul style="list-style-type: none"> • LV Thrombus • Significant AI • Mechanical AV • Severe PAD 	<ul style="list-style-type: none"> • VSD • Significant AI • Left atrial thrombus 	<ul style="list-style-type: none"> • Severe PAD • Significant AI • Aortic Dissection
Complications	<ul style="list-style-type: none"> • Limb Ischemia • Bleeding • Aortic dissection • Thrombocytopenia 	<ul style="list-style-type: none"> • Limb Ischemia • Bleeding • Ventricular arrhythmia • LV perforation 	<ul style="list-style-type: none"> • Limb Ischemia • Bleeding • Intra-arterial shunt • Air emboli 	<ul style="list-style-type: none"> • Limb Ischemia • Bleeding • Stroke • LV distention

Increasing Level of Support →

Review of short-term mechanical circulatory support devices including intra-aortic balloon pump (IABP), Impella, TandemHeart, and venoarterial extracorporeal membrane oxygenation (VA-ECMO). Presented are their expected augmentation of cardiac output, their advantages and disadvantages, contraindications and complications (Supplemental Ref. 47,53,54,56). AAA = abdominal aortic aneurysm; AI = aortic insufficiency; CO = cardiac output; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; PAD = peripheral artery disease; VSD = ventricular septal defect; other abbreviations as in Figure 1

which the venous and arterial cannulae are placed directly in the right atrium and ascending aorta, respectively (Supplemental Ref. 56). The hemodynamic improvements associated with VA-ECMO commonly restore end-organ perfusion. However, VA-ECMO flow delivered retrograde to the aorta increases LV afterload. LV preload may also increase as a result of incomplete capture of venous return. Clinically, this can result in LV distention which manifests as pulmonary edema with worsening oxygenation, increases the risk of LV thrombus formation as a result of stasis in the nonejecting LV, and is associated with lower rates of myocardial recovery (Supplemental Ref. 57). Thus, some centers

attempt to use “partial flow” VA-ECMO, whereby flow is minimized to sustain blood pressure and end-organ perfusion while inotropic agents are concomitantly administered to ensure ejection of blood from the LV (Supplemental Ref. 58). If LV distention develops, the LV can be unloaded percutaneously with the placement of an Impella or surgically with placement of a vent (Supplemental Ref. 59). Other common complications of VA-ECMO include acute limb ischemia (in the case of peripheral cannulation), stroke, bleeding, and infection.

Once temporary mechanical circulatory support has been deployed, biventricular function should be reassessed with focused echocardiography and

FIGURE 6 Relative and Absolute Contraindications to Advanced HF Therapies

Absolute Contraindications	Relative Contraindications	Relative Contraindications	Absolute Contraindications
<ul style="list-style-type: none"> Systemic Illness with a life expectancy < 2 years Fixed Pulmonary Hypertension 	<ul style="list-style-type: none"> Age > 72 years old Any active infection (with the exception of device related infections in VAD) Severe diabetes with end-organ damage Severe peripheral vascular disease or cerebrovascular disease Active peptic ulcer disease Morbid obesity or cachexia Creatinine > 2.5 or creatinine clearance < 25 FEV1 < 40% expected Difficult to control hypertension Irreversible neurologic or neuromuscular disorder Active mental illness or psychosocial instability Medical nonadherence Drug, tobacco, alcohol use within 6 mos. Liver dysfunction with total bilirubin > 2.5, serum transaminases > 3x normal, and/or INR >1.5 off warfarin Heparin induced thrombocytopenia within 100 days 	<ul style="list-style-type: none"> Age > 80 Morbid obesity or cachexia Musculoskeletal disease that impairs rehabilitation Active systemic infection or prolonged intubation Untreated malignancy Severe peripheral vascular disease or cerebrovascular disease Drug, tobacco, alcohol use within 6 mos. Impaired cognitive function Psychosocial instability 	<ul style="list-style-type: none"> Irreversible hepatic disease Irreversible renal disease Irreversible neurologic or neuromuscular disorder Medical nonadherence Active mental illness or psychosocial instability

Heart Transplantation

Left Ventricular Assist Device

Review of the absolute and relative contraindications for heart transplantation and left ventricular assist device therapy ([Supplemental Ref. 62,119,120](#)). FEV1 = 1-min forced expiratory volume; HF = heart failure; INR = international normalized ratio; VAD = ventricular assist device.

frequent assessment of invasive hemodynamics in order to determine which devices can be safely weaned and which patients should be evaluated for escalation of support.

LONG-TERM MANAGEMENT OF ADVANCED HF: HEART TRANSPLANTATION

Long-term advanced HF therapies should be considered for patients in whom guideline-directed medical and device therapy has failed to result in sufficient hemodynamic improvement to ameliorate symptoms or preserve end-organ function. For patients without options for more durable treatments, long-term inotropic therapy may be administered to improve quality of life and symptom burden ([Supplemental Ref. 60](#)). Although survival on chronic inotropic support remains poor, it does appear to be improving in the current era with 1-year estimated survival now close to 40% ([Supplemental Refs. 42,61](#)).

Heart transplantation remains the gold standard therapy for selected patients with demonstrable improvements in quality of life, functional status, and longevity when compared with conventional therapy ([Supplemental Refs. 11,22](#)). One-year survival

following cardiac transplantation is now >90% with a median survival of 12.2 years, though patient selection remains a critical component of achieving satisfactory post-transplant outcomes ([Figure 7](#)) ([Supplemental Refs. 62-68](#)). The United Network of Organ Sharing recently approved a major revision to the heart allocation policy intended to decrease waitlist mortality, particularly for the sickest candidates, and improve equitable distribution of donor hearts by introducing more granular stratification of patients, broader geographic sharing, mandatory reassessment of high-priority patients, and standardizing definitions ([Supplemental Ref. 69](#)) ([Figure 8](#)). Important features of the new allocation system include higher priority status for temporary mechanical circulatory support and deprioritization of stable outpatients with durable LVADs. The new allocation system has not assigned higher priority to patients with nondilated myopathies including restrictive and hypertrophic cardiomyopathy despite suggestion of increased waitlist mortality in this cohort ([Supplemental Ref. 70](#)).

Organ scarcity continues to limit the number of transplantations performed annually. In the United States, a recent increase in donor availability has been driven by the opioid epidemic ([Supplemental Ref. 71](#)).

FIGURE 7 Evaluation of Heart Transplant Candidates**Evaluation of the Heart Transplant Candidate:**

- Clinical History and Physical Examination
- Laboratory Evaluation: Complete Blood Count, Basic Metabolic Panel, Liver Function Tests, Urinalysis, Coagulation Studies, Thyroid Evaluation, Urine Drug Screen, Alcohol Level, HIV Testing, Hepatitis Testing, Tuberculosis Screening, CMV IgG and IgM, RPR/VDRL, Panel Reactive Antibodies, ABO and Rh Blood Type, Lipids, Hemoglobin A1c
- Chest X-Ray, Pulmonary Function Testing
- EKG
- Right and left heart catheterization
- Cardiopulmonary exercise testing
- Age appropriate malignancy screening
- Psychosocial evaluation (including substance abuse history, mental health, and social support)
- Financial Screening

Components of the evaluation of candidates for heart transplantation as suggested by the International Society for Heart and Lung Transplant Guidelines (Supplemental Refs. 62-67,121). CMV = cytomegalovirus; ECG = electrocardiogram; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; RPR/VDRL = rapid plasma reagin/venereal disease research laboratory.

In multiple analyses, post-transplant outcomes of these higher-risk donors appear to be comparable to those with other causes of death (Supplemental Ref. 72). With the advent of direct-acting, curative antiviral therapy, numerous transplant programs have also developed protocols to use hearts from hepatitis C (HCV)-positive donors and have reported excellent post-transplant outcomes with elimination of HCV viremia and presumed “cure” (Supplemental Refs. 73,74). Despite early enthusiasm for this approach, questions about cost-effectiveness and long-term outcomes (including allograft vasculopathy) remain (Supplemental Ref. 75). Another effort to increase the number of cardiac donors is expansion of organ donation after circulatory death (DCD). The principles of DCD donation involve the declaration of circulatory death followed by a waiting period determined legally and ethically by the country in which the donor is located—typically ranging from 2 to 5 min (Supplemental Ref. 76). Since the first successful DCD heart transplant in 2014, international experience suggests post-transplant outcomes are comparable to traditional donors (Supplemental Refs. 77,78). Ex-vivo perfusion of donor hearts, which maintains the donor heart in a warm and contracting state during transport, has been pivotal in expanding DCD donation and may facilitate safe use of organs that require extended travel times (Supplemental Refs. 79,80).

Although post-transplant survival remains excellent, the complex milieu of ischemia, host immunological recognition of the transplanted organ, systemic infections, medications, and traditional

risk factors for coronary disease limit the true potential of heart transplantation. Primary graft dysfunction (PGD)—acute failure of the allograft to support the circulation in the absence of rejection or other identifiable cause—continues to contribute to early post-transplant mortality (Supplemental Ref. 81). Management of PGD involves prompt intraoperative identification, early institution of VA-ECMO support, and post-operative titration of immunosuppression, including avoidance of induction therapy in the absence of sensitization, renal failure, or other high-risk features (Supplemental Ref. 81). The majority of PGD patients treated with VA-ECMO are weaned to recovery (Supplemental Ref. 82).

Additional targets for improving post-transplant outcomes include management of both cellular and humoral rejection, personalized immunosuppression, and achieving an optimal balance between the two. Although endomyocardial biopsy remains the standard for detecting rejection in the early post-transplant period, gene expression profiling with Allomap (CareDx, Brisbane, California) and measurement of donor-derived cell-free DNA are being increasingly used to facilitate noninvasive screening for rejection (Supplemental Refs. 83,84). Current ISHLT guidelines support the use of gene expression testing for noninvasive monitoring of rejection for appropriate low-risk patients between 6 months and 5 years after heart transplantation (Supplemental Ref. 85).

Long-term graft survival is also limited by the development of cardiac allograft vasculopathy (CAV),

FIGURE 8 Revised UNOS Heart Allocation System

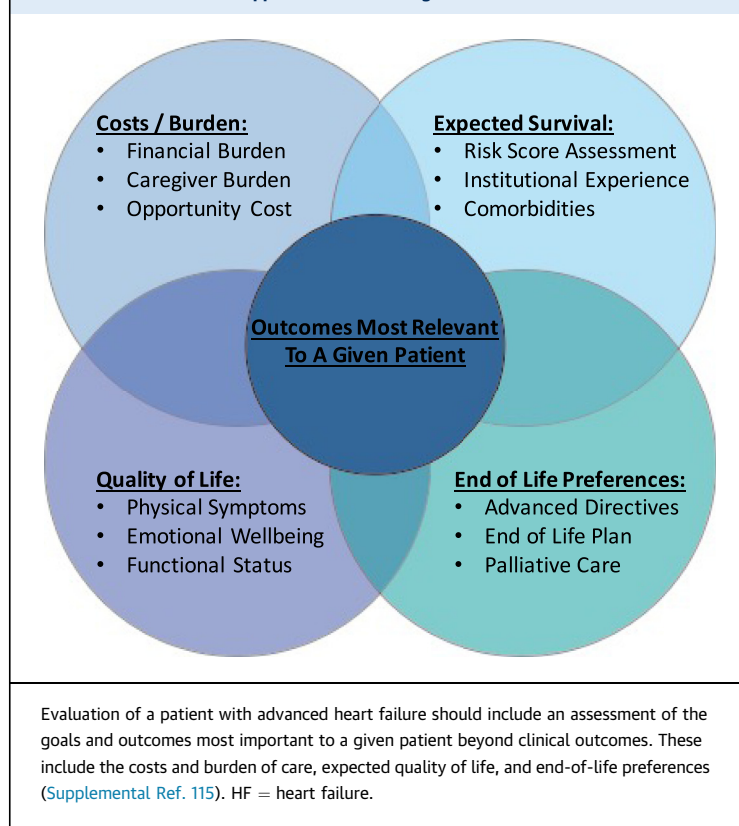
Tier	
1.	<ul style="list-style-type: none"> i. VA ECMO (up to 7 days) ii. Non-Dischargeable BIVAD iii. Mechanical circulatory support with life threatening ventricular arrhythmia
2.	<ul style="list-style-type: none"> i. Intra-aortic balloon pump (up to 14 days) ii. Acute percutaneous endovascular circulatory support (up to 14 days of support) iii. Ventricular tachycardia / Ventricular Fibrillation, mechanical circulatory support not required iv. Mechanical circulatory support with device malfunction / device failure v. Total Artificial Heart vi. Dischargeable BIVAD or RVAD
3.	<ul style="list-style-type: none"> i. LVAD for up to 30 days ii. Multiple Inotropes of Single High-Dose Inotrope With Continuous Hemodynamic Monitoring iii. Mechanical Circulatory Support with Device Infection iv. Mechanical Circulatory Support with Thromboembolism v. Mechanical Circulatory Support with Device Related Complications Other Than Infection, Thromboembolism, Device Malfunction/Failure, and Life Threatening Ventricular Arrhythmias
4.	<ul style="list-style-type: none"> i. Diagnosis of Congenital Heart Disease (CHD) with: <ul style="list-style-type: none"> a. Unrepaired/incompletely repaired complex CHD, usually with cyanosis b. Repaired CHD with two ventricles c. Single ventricle repaired with Fontan or modifications ii. Diagnosis of ischemic heart disease with intractable angina iii. Diagnosis of hypertrophic cardiomyopathy iv. Diagnosis of restrictive cardiomyopathy v. Stable LVAD patient after 30 days vi. Inotropes without hemodynamic monitoring vii. Diagnosis of amyloidosis viii. Retransplant
5.	<ul style="list-style-type: none"> i. Approved combined organ-transplants: heart-lung, heart-liver, heart-kidney
6.	<ul style="list-style-type: none"> i. All remaining active candidates
7.	<ul style="list-style-type: none"> i. Inactive / Not Transplantable

The updated United Network of Organ Sharing (UNOS) Heart Allocation System, which went into effect in October of 2018 ([Supplemental Ref. 69](#)). BIVAD = biventricular assist device; RVAD = right ventricular assist device; other abbreviations as in [Figures 2 and 5](#).

a disease of the coronary arteries characterized by widespread fibrointimal hyperplasia affecting up to 75% of patients 3 years post-transplant ([Supplemental Ref. 86](#)). The use of intravascular ultrasound as part of routine coronary angiography has increased the sensitivity of screening, with CAV found in almost one-half of patients at 1 year using intravascular ultrasound as compared with 10% to 20% using standard coronary angiography alone ([Supplemental Ref. 87](#)). After transplantation, aggressive lipid-lowering therapy should be prescribed, with pravastatin in particular shown to improve low-density lipoprotein cholesterol and triglyceride levels, increase high-density lipoprotein cholesterol, reduce intimal thickness and CAV, as well as improve survival ([Supplemental Ref. 88](#)). Newer antiproliferative agents, mycophenolate mofetil, sirolimus, and everolimus, have also been shown to be more efficacious in the prevention of CAV compared with azathioprine ([Supplemental Refs. 89,90](#)).

LONG-TERM MANAGEMENT OF ADVANCED HEART FAILURE: MECHANICALLY ASSISTED CIRCULATION

The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive HF) trial was the first randomized study to describe the benefits of LVAD support compared with conventional medical therapy in patients with end-stage HF ineligible for heart transplantation ([Supplemental Ref. 61](#)). Since the REMATCH trial, LVAD therapy has evolved rapidly, and with each subsequent generation of devices has come improvements in durability, device complications, and survival ([Supplemental Ref. 91](#)). As of 2017, over one-half of heart transplant recipients reported in the ISHLT registry had been supported with mechanically assisted circulation ([Supplemental Ref. 92](#)). The INTERMACS registry reports that over 3,000 LVADs are implanted annually in the United States with

FIGURE 9 Personalized Approach to Addressing Patient Goals in Advanced HF

nearly one-half of those being for destination therapy (DT) (6).

The most recent device to gain Food and Drug Administration approval for bridge to transplant and DT indications is the HeartMate 3 (Abbott, Chicago, Illinois). This fully magnetically levitated centrifugal pump was engineered to improve hemocompatibility, reduce stasis, and prolong durability. The pump is programmed to generate an artificial “pulse,” varying speeds from the set RPM by 2,000 every 2 s to produce changes in flow and pressure in an effort to reduce the risk of pump thrombosis. The HeartMate 3 was compared with the prior generation HeartMate II axial flow pump in the MOMENTUM 3 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with Heartmate 3) study. When assessing the primary endpoint of survival free from disabling stroke or the need to remove or replace the device, the HeartMate 3 was shown to be noninferior to the HeartMate II, with significantly lower rates of device exchange resulting from pump thrombosis. When groups were compared after 2 years of support, 76.9% of patients supported with the HeartMate 3 achieved the primary endpoint as compared with 64.8% of patients with the older-

generation axial flow pump (hazard ratio: 0.84, 95% confidence interval: 0.78 to 0.91; $p < 0.001$) (Supplemental Ref. 93). Freedom from hemocompatibility-related events, including nonsurgical bleeding, thromboembolic events, pump thrombosis, and neurologic events, was also superior in HeartMate 3 as compared with the HeartMate II: a result that was particularly prominent in patients <65 years of age at the time of implantation (Supplemental Ref. 94).

Adverse events remain the Achilles heel of LVAD technology. In the MOMENTUM 3 trial, 10% of patients supported with the HeartMate 3 experienced a stroke (7% disabling), 43% experienced episodes of nonsurgical bleeding, 24% experienced a drive-line infection, and 32% exhibited clinical signs of RV failure. These device complications contribute to significant on-device morbidity and mortality, and may necessitate re-evaluation of patients for transplant candidacy.

In patients ineligible for heart transplantation, use of LVAD as DT continues to grow (Supplemental Ref. 95). In these patients, evaluation of INTERMACS profiles can aid in identifying optimal timing of device implantation. The prospective ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management) study evaluated patients with advanced HF who were not treated with inotropes (INTERMACS profiles 4 to 7) and demonstrated superior survival and functional status compared with those medically managed, with the tradeoff of increased adverse events and hospitalizations (Supplemental Refs. 96,97). It is important to remember, however, that no universal guideline exists to inform patient selection for LVAD therapy, and INTERMACS profiles are likely insufficient to quantify a patient's risk alone. Other factors that must be taken into consideration include end-organ function, age, sex, frailty, and need for concomitant procedures (Supplemental Ref. 98). In addition, a thorough and standardized psychosocial evaluation can help to ensure patient satisfaction with LVAD therapy and decrease device-related complications (Supplemental Refs. 99,100). Low socioeconomic status alone, should not preclude LVAD candidacy (Supplemental Refs. 101).

Early data from LVAD studies suggest that some patients are capable of achieving partial or complete recovery of LV function during LVAD support (Supplemental Ref. 102). Hypertrophy, beta-receptor sensitivity, collagen metabolism, and cytoskeletal structure all improve with mechanical unloading (Supplemental Refs. 103-105). Despite these encouraging molecular changes, contemporary studies suggest that <5% of patients with LVAD have their device

explanted for myocardial recovery ([Supplemental Ref. 106](#)). Multiple centers have developed individualized recovery protocols to identify patients most likely to benefit from aggressive LV unloading and neurohormonal blockade to facilitate successful device explant. The weighted I-CARS score, which includes age <50 years, nonischemic etiology, time from cardiac diagnosis <2 years, absence of implantable cardioverter-defibrillator, creatinine <1.2 mg/dL, and LV end-diastolic dimension <6.5 cm has been shown to effectively risk stratify patients for their probability of myocardial recovery ([Supplemental Ref. 107](#)). Ongoing translational research is focusing on the biochemical and molecular pathways responsible for reverse remodeling in an effort to develop more targeted therapeutic agents to facilitate sustained improvement in LV function ([Supplemental Ref. 108](#)).

The future of LVAD therapy will likely see a shift toward less invasive implantation strategies (i.e., via lateral thoracotomy approach) as well as adoption of fully implantable devices (i.e., Leviticus FiVAD, Leviticus-Cardio, Petah Tikva, Israel) and remote monitoring capabilities that may improve outcomes, particularly in high-risk individuals ([Supplemental Refs. 109,110](#)).

LIVING WITH ADVANCED HF

Although the aforementioned short- and long-term treatment strategies are intended to increase longevity, they do little to ameliorate the symptom burden and psychosocial distress that disproportionately affects patients dying from HF ([Supplemental Ref. 111](#)). Patients often have limited insight into the severity of their disease process and expected mortality—particularly those who are not candidates for advanced therapies ([Supplemental Refs. 112-114](#)). Although most clinical trials have focused on mortality and rehospitalization, many patients value quality of life and symptom relief over longevity ([Figure 9](#)) ([Supplemental Ref. 115](#)). As a result, palliative care—a multidisciplinary approach to assessing and improving quality of life and symptom management—is being increasingly integrated into standard medical care to improve patient-centered outcomes. A randomized trial of palliative care in advanced HF recently demonstrated significant improvements in quality-of-life metrics, anxiety, and depression as compared with usual care alone ([Supplemental Ref. 116](#)). As such, integration of palliative care with conventional medical therapy in patients with advanced HF is recommended by multiple

professional societies. Importantly, palliative care and advanced therapies are not mutually exclusive, but rather should be employed in concert to ensure the best possible outcomes for patients and their families ([Supplemental Ref. 117](#)). Palliative care intervention before LVAD implantation or heart transplantation is crucial in helping patients articulate their goals and health states they would find unacceptable. In this way, patients and their families can feel empowered to make difficult decisions to honor their wishes at the end of life. Despite some progress in this area, there remains much work to be done, as only 34% of patients with HF are referred for palliative care in their last month of life, and mean time from referral to death is <2 weeks ([Supplemental Ref. 118](#)).

FUTURE DIRECTIONS AND CONCLUSIONS

The syndrome of advanced HF remains an epidemiological, clinical, and financial challenge for patients, physicians, and policy makers. Recent improvements in advanced therapies have helped more patients live longer, but have substantially increased clinical complexity and cost of care. Although temporary mechanical support has revolutionized the management of CS, the ongoing lack of prospective, randomized controlled trial data limits our understanding of the risks and benefits of this technology for a given patient. As use of durable support increases, criteria and guidelines for patient selection must be standardized in order to curb costs of care and improve post-implantation outcomes. In transplantation, work to expand the donor pool must continue while we pursue basic and translational research to understand how to improve allograft longevity by preventing and treating PGD and CAV. Personalized approaches to immunosuppression are also needed to maximize graft tolerance and minimize infectious risk. Ongoing research focusing on myocardial recovery is desperately needed, because biochemical pathways capable of reversing, if not preventing, HF would radically change our approach to care. Lastly, we must continue to integrate patient-centered, symptom-based palliative care into our advanced HF paradigm in an effort to help patients with advanced HF not only live longer, but live better.

ADDRESS FOR CORRESPONDENCE: Dr. Joseph G. Rogers, 10 Duke Medicine Cir, Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710. E-mail: joseph.rogers@duke.edu.

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APPENDIX For a supplemental figure and an expanded reference list, please see the online version of this paper.



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