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Patient Selection for Destination LVAD Therapy: Predicting Success in the Short and Long Term

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Abstract

Purpose of Review In this review, we discuss risk assessment of advanced heart failure (HF) patients as a referral guide for advanced HF therapies, including left ventricular assist device (LVAD) support and cardiac transplant.

Recent Findings The frequency of LVAD implantation for the purpose of permanent "destination" therapy is growing and survival on LVAD support is now approximating 50% at 5 years. Ambulatory HF patients with HF functional limitations, end-organ dysfunction, inability to tolerate HF medications, frequent cardiac admissions, and ventricular dysrhythmias are at high risk for mortality with medical management alone. Simultaneously, LVAD survival is superior in patients implanted prior to the onset of cardiogenic shock and/or multisystem dysfunction.

Summary Early referral (< 7% annual predicted mortality) of patients with systolic heart failure to an advanced heart failure specialist is critical for achieving long-term survival.

Keywords Systolic heart failure · LVAD · Mortality · Risk prediction

Introduction

Heart failure (HF) is a prevalent condition with a very diverse patient phenotype and diffuse mortality ascription. Patients with severe symptomatic systolic HF fall into American College of Cardiology/American Heart Association (ACC/AHA) stage C or stage D categorization. While only ~ 10% of those living with systolic HF have New York Heart Association (NYHA) functional class IIIb-IV symptoms, the survival in this subgroup of patients is universally poor, ranging from 25 to 64% at 1 year [1–3]. Further, the prevalence of stage D HF is increasing, and it is estimated that ~ 5% of outpatients with stage C HF will progress to stage D HF each year, yielding an increase of 100,000 patients [4] with stage D HF per year, and an estimated overall prevalence of 250,000–300,000 patients.

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The growth in the prevalence of advanced HF across the globe and the marked improvement in outcomes with recent advancements in HF interventions have led to the development of the advanced heart failure multidisciplinary subspecialty, which is dedicated to the diagnosis and multidisciplinary management (medical and surgical) of these very complex patients. Management options for those with advanced HF include cardiac transplant, mechanical circulatory support, and palliative care/hospice. While cardiac transplant is the gold standard intervention for carefully selected patients with stage D HF, the resource limitation of transplant and stringent candidacy criteria restricts this offering to only 2000–2800 US adults a year [5]. For many patients with significant comorbidities or advanced age, palliative care with or without hospice services may be the best management approach. Over the last decade, however, the evolution of mechanical circulatory support (MCS), most commonly in the form of left ventricular assist device (LVAD) support, has offered many with end-stage HF a third consideration for HF management. LVAD support can be used until the time of transplant (bridge to transplant therapy) or as a permanent "destination" therapy without the goal for transplant. To date, over 19,000 individuals in the USA have received a Food and Drug Administration (FDA)-approved durable LVAD for the management of recalcitrant HF, yielding a present US implant volume of

~ 2400 devices per year [6••]. The largest growth in the field has been noted in individuals implanted for destination therapy, increasing from 36 to 49% of LVAD implants between 2010 and 2017. In concert with the increases in implant volume, 1-year survival has improved from 80% in 2012 to 83% in 2017 and mean overall survival has increased from 48 months in 2012 to 60 months in 2017, leading to more and more patients living within the community on chronic LVAD support [6••, 7].

The enthusiasm derived from improved LVAD survival has been tempered, however, by a persistent prevalence of serious complications, including stroke, infection, device thrombosis, and right HF. The readmission frequency after LVAD is ~ 50% at 3 months and ~ 80% at 1 year. While the early postoperative period (first 90 days) offers the highest hazard for each of these complications, the instantaneous risk for most major adverse events never reaches zero and the risk for many complications (such as right HF and device-related infection) begins to increase again with prolonged support [7].

Assessing Mortality Risk in Patients With Systolic Heart Failure

In order to ensure optimal outcomes for patients with progressing systolic HF, and to ensure all advanced HF management options have been appropriately considered, the ACC and the AHA have added recommendations for advanced heart failure specialty referral to HF management guidelines [8••, 9]. Thus, for general practitioners, the most imperative step in managing patients with advanced HF is to assess their risk of death with ongoing medical management of HF so that appropriate, timely advanced HF referral can be initiated.

While survival in patients with severe systolic HF is on average poor, patient phenotypes are highly heterogenous, leading to marked patient-level variability in survival. For example, patients with cardiogenic shock with or without use of temporary circulatory support have uniformly poor survivals of 35–50% at discharge while those who are less critically ill but dependent on home inotropes have marginally better survivals of 25–50% at 1 year [10]. The most challenging patients to prognosticate risk are those in the outpatient setting who are ambulatory with severe left ventricular dysfunction without an inotrope requirement. These patients are most commonly grouped into the stage C category (systolic dysfunction with present or past HF clinical signs and symptoms). However, some within the stage C HF category have very poor short-term survival and for others, the transition to the "refractory" HF stage D category is often nebulous. In the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) study, ambulatory outpatients on optimal medical management with NYHA Class IIIb/IV systolic (ejection fraction ≤ 25%) HF, ≥ 1 hospitalization in a year for HF, and 6-min walk distance < 300 m had a 1-year survival of 63% [1]. At 2 years, only 41% were alive on medical therapy and 22% received an LVAD implant [11•].

Thus, estimating such mortality risk in the diffuse systolic HF population requires careful (re)assessment of patient functional capacity, laboratory values, vitals, and clinical history. Several clinical trials, registries, and cohort studies have identified risk factors for mortality in patients with symptomatic systolic HF [12–17]. Using such data, the ACC has developed the acronym "I NEED HELP" to help guide practitioners on when advanced HF consultations should be considered. The high-risk features include need for Intravenous inotropes, NYHA class IIIb/IV heart failure, End-organ dysfunction, EF ≤ 35%, Defibrillator shocks, recurrent Hospitalizations, Edema despite escalation of diuretics, Low systolic BP, and Progressive intolerance of guideline-directed medical therapies [8••].

While large clinical trials and national databases are available to provide patients population averages for survival with HF, the large variability in survival makes patient-specific risk estimates essential for thorough shared decision-making prior to transplant, LVAD, or hospice referral. In addition, risk prediction is critical to clinicians, assisting with patient selection to avoid futile LVAD or transplant offerings. To allow for a better characterization of an individual patient's risk of death from medical managed HF, various risk prediction models have been developed [14–16, 18, 19], which are outlined in Table 1. When evaluating the risk scores discussed below, it is important to select a model derived from a population that mirrors your patient's characteristics. Importantly, no single HF model has excellent accuracy in risk prediction; thus, the HF risk models should be used to supplement—but not replace—clinical decision-making.

The Seattle Heart Failure Model (SHFM) is the most extensively studied and widely employed HF risk model [14]. The SHFM was derived from 1125 patients enrolled into the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study [20], which required a left ventricular ejection fraction ≤ 30% and NYHA class IIIb-IV symptoms for inclusion. Because HF medication use (angiotensin inhibitor, aldosterone antagonist, and β-blockers) and application of defibrillator/resynchronization therapies were not commonplace in the 1990s, the β-coefficients for SHFM risk score calculation were estimated from large published studies [14]. Correlates of mortality identified by the SHFM include patient age, NYHA class III/IV, escalating diuretic dose, anemia, lymphopenia, hyponatremia, and hyperuricemia (Table 1) [14]. After entering data into an online SHFM calculator [21], practitioners are given patient-level estimates of HF mortality at 1 and 5 years. While the SHFM has been independently externally validated, the model's accuracy in the advanced HF population remains suboptimal. For example, when the SHFM was applied to the ROADMAP cohort discussed

Table 1 Heart failure risk prediction models and their variables

Author	Risk model	*N*	Markers	Time horizon
Levy [14]	Seattle Heart Failure Model	1125	SBP, age, gender, EF, weight, NYHA class, etiology, diuretic dose, use of statin, beta blocker, RAAS inhibition, allopurinol, metolazone, furosemide equivalence dosing, potassium sparing diuretic, defibrillator, BiV pacing, Na, cholesterol, Hgb, % lymphocytes, uric acid	3 years
Pocock [16]	MAGGIC	39,372	Cr, SBP, age, gender EF, BMI, NYHA class, current smoker, DM, COPD, HF diagnosis > 18 months, use of B-blocker, ACEi/ARB	3 years
O'Connor [15]	OPTIMIZE-HF	4402	Cr, SBP, age, weight, Na, lower extremity edema, reactive airway disease, depression, use of B-blocker, lipid lowering therapy	90 days
Fonarow [18]	ADHERE	65,275	BUN, SBP, HR, age	In hospital
Peterson [19]	GWTG-HF Risk Score	39,783	BUN, SBP, HR, Age, Na, Black race, COPD history	In hospital

ACEi, angiotensin-converting enzyme inhibitor; *ARB*, aldosterone receptor blocker; *Bi-V*, biventricular; *BMI*, body mass index; *BUN*, blood urea nitrogen; *COPD*, chronic obstructive airway disease; *Cr*, creatinine; *DM*, diabetes mellitus; *EF*, ejection fraction; *GWTG*, Get with the Guidelines; *HF*, heart failure; *Hgb*, hemoglobin; *HR*, heart rate; *Na*, sodium; *SBP*, systolic blood pressure

above, the SHFM was predictive of overall survival (C-statistic 0.71) but under-estimated clinical deterioration necessitating LVAD [22]. The latter is critical when evaluating patients within the large, diverse stage C HF subpopulation. Reduced model performance is likely multifactorial and may be related to the less contemporary patient sample from which the SHFM was derived; exclusion of patients on inotropes; and model derivation from a clinical trial cohort which was exclusive of a "sick patient" phenotype. The Meta-Analysis Global Group In Chronic HF (MAGGIC) is another risk model, derived from 39,272 patients enrolled into 30 different HF studies [16]. While the MAGGIC derivation cohort included patients with HF with preserved ejection fraction, the average MAGGIC sample mortality was 40% over 2.5 years of follow-up. Correlates for mortality using the MAGGIC score include age, renal function, blood pressure, and noncardiac comorbidities (Table 1) [16]. High-risk ambulatory HF patients, regardless of the model chosen, have evidence of perturbations in renal function (even mild). Furthermore, patients with recurrent ventricular dysrhythmias, especially those who have failed ventricular tachycardia ablation, are very high risk for mortality and should be considered for advanced HF referral regardless of ventricular ejection fraction, renal function, blood pressure, or NYHA class [23, 24].

Finally, objective measures of patient functional capacity are integral to assessing the true impact of HF on patients' physical activity. Such measures also provide important prognostic information. The 6-min walk test is a simple and well-validated measure for assessing functional capacity. In general, a 6-min walk test distance < 300 m is considered to be a marker of increased mortality risk in patients with systolic HF [25]. Cardiopulmonary exercise testing is a less widely available tool but provides critical prognostic information; is a precise estimation of patient metabolic equivalents (METS) achieved; and can identify other contributors to HF exercise intolerance, including pulmonary limitations and chronotropic incompetence. In general, a reduced peak oxygen uptake ($pVO_2 \leq 50\%$ patient predicted) or impaired ventilatory efficiency (Ve/VCO_2 slope > 34) on cardiopulmonary stress testing identifies a high-risk ambulatory HF patient independent of NYHA class [26].

Assessing a Patient's Risk of Death From LVAD Surgery

Patients with a predicted HF mortality of ≥ 7% at 1 year should be considered for advanced HF referral. This threshold is chosen because it approximates the risk associated with cardiac transplant surgery and promotes early advanced HF referral. Early referral is critical to (a) foster the development of a relationship with the advanced HF program that is necessary for assessing patient compliance for transplant/LVAD candidacy; (b) to allow application of LVAD/transplant therapy prior to onset of severe organ deterioration; and (c) to ensure adequate opportunity for LVAD/transplant patient education as part of shared decision-making prior to patient loss of decision capacity from HF.

While LVAD therapy has been shown to improve survival, quality of life, and functional capacity, all patients do not enjoy such success. In addition to high operative mortality risks, the occurrence of adverse events on long-term LVAD support can have a marked impact on patient quality of life. Thus, the explanation of LVAD therapy as part of the shared decision-making process relies on presenting LVAD candidates and caregivers with a reasonable estimate of patient-specific morbidity and mortality risk. Like the HF models discussed above, several risk models have been developed to improve patient-level risk assessment for LVAD surgery. These models are outlined below and carry the same limitations in discrimination and/or calibration for patient risk assessments.

LVAD Risk Models for Predicting Operative Survival

Prognosticating short- and long-term survival after LVAD implant is very complex and often imprecise. Similar to the HF risk models, patients with evidence of preoperative renal dysfunction, hepatic congestion and/or right ventricular dysfunction, advanced age, poor functional capacity, and poor nutrition have higher operative mortality risk during LVAD surgery. In addition, mortality is greatly impacted by the coexistence of other concomitant medical conditions (e.g., pulmonary disease) as well as complications encountered during the perioperative period (e.g., pneumonia, bleeding, right ventricular failure) and those that develop as a result of LVAD support (e.g., stroke). Table 2 outlines the various models presently available for operative risk stratification of LVAD candidates [27•, 28–31, 32•, 33–37]. The scores differ in the LVAD device(s) used for score derivation, era of patient management, and primary outcome of interest. Included in the table are those models developed with the intent of predicting postLVAD right ventricular failure. Given the high mortality associated with right ventricular failure, these models tend to also identify patients with high LVAD operative mortality [35, 37] and risk variables overlap with those in the mortality risk prediction models.

The HeartMate II Risk Score (HMRS) [28] is the most widely known score in the era of continuous flow LVAD technology. The HMRS was devised from a sample ($n = 583$) of the combined destination therapy and bridge to transplant HeartMate II (Abbott, Abbott Park, IL) LVAD clinical trials and then was validated using a separate patient sample ($n = 539$) from the same trials [27•]. The HMRS is calculated from the following preoperative patient variables: serum creatinine (mg/dl), albumin (g/dl), INR, age (years), and center surgical volume. Using the HMRS, patients can be divided into quartiles of mortality risk ranging from very low (< 5% 90-day mortality) to high (> 20% 90-day mortality). Criticisms of this score were primarily directed at the fact that it was developed from a selected subset of LVAD patients who met requisite clinical trial inclusion/exclusion criteria and the score also included surgical clinical trial implant volume, which may not have valid risk attribution with ongoing surgical device implant experience. The modified HMRS attempted to address these concerns, dropping the input of center volume. The score was evaluated in a cohort of 9733 INTERMACS registry patients on continuous flow LVAD support (mostly a HeartMate II cohort) and separately in 382 patients undergoing HVAD (Medtronic, Minneapolis, MN) implant as part of the bridge to transplant continuous access protocol. The odds of 90-day mortality increased by 1.3 (1.3–1.5) for each unit increase in the adjusted HMRS (model AUC 0.64 ± 0.01) within the INTERMACS cohort and 1.7 (1.02–2.95) for each unit increase in the adjusted HMRS in the HVAD cohort. The AUC, a measure of discrimination, was only modest at best. Other groups have noted lower AUC values on external validation of the original HMRS [38].

While not originally intended for use the HF population, the Model for End-Stage Liver Disease (MELD, composed of serum creatinine, bilirubin, sodium, and INR) and the MELDx (omitting INR) have also been shown to be predictive of LVAD operative mortality. The laboratory variables comprising the MELD score again highlight the impact of multisystem dysfunction (liver and/or right ventricle and renal) on LVAD outcomes, such that higher scores confer worse survival [36, 39].

Finally, risk prediction from large databases with use of machine learning is a growing focus in the LVAD field (Table 2, [32•, 40]). Machine-derived models, while still in their infancy, have the potential to provide more accurate estimates of patient-level mortality than risk scores derived using traditional regression statistics. However, machine-derived model accuracy in LVAD risk prediction will be reliant on tallying all the necessary data that impart mortality risk in appropriate detail and their utility will be beholden on the local specialist's ability to apply the complex modeling to the individual patient during a clinical encounter.

Predicting Long-term Survival on LVAD Support

The average survival after LVAD implant presently approximates 5 years [6••]. Few studies, however, have identified preoperative attributes of long-term success on LVAD support [40, 41]. Since operative survival is obligatory for long-term survival, the risk factors discussed above in predicting short-term mortality certainly apply. When the HeartMate II bridge to transplant and destination therapy cohorts were limited to those patients surviving the operative (90 day) window, only patient age and center experience were associated with longer term survival [27•]. The Penn-Columbia Risk Score was developed to generate a tiered risk for 1-year mortality after LVAD [41]. The variables in the score include patient age, body mass index, serum bilirubin, creatinine, and preoperative echocardiography (measures of aortic insufficiency and right ventricular function). Notable limitations to the model include the fact that operative deaths were not excluded, independent validation is lacking, and risk prediction was capped at 1-year postVAD. The application of LVAD therapy to the less ill will rely on developing a means to predict which advanced HF patients will have a survival of > 3–5 years on device support.

Perhaps more importantly, the response to LVAD therapy extends beyond survival. As with all therapies, determination of success depends upon quality of life (QoL) following implementation of an intervention. Factors that determine both QoL and functional capacity (FC) following LVAD are area of increased, with several groups evaluating predictors of positive/negative responses to MCS as well as the more abstract concept for frailty and its effect on LVAD outcomes [17, 42–49, 50•]. Frailty as a clinical entity is a complex and multifaceted patient adjective which can be phenotyped as an increase in physiologic vulnerability with an associated

Table 2 Left ventricular assist device risk scores and their variables

	Device(s) Studied	Clinical Variables	Hemodynamic	Labs
Survival Risk Prediction Models				
DTRS (29)	XVE	Use of vasodilator therapy, absence of inotrope	Mean pulmonary pressure ≤25 mmHg	**Albumin <3.3 g/L**, **BUN >51 U/dL**, **INR >1.1**, Platelet <149 IU/L, hematocrit <35%, **AST >45 IU/L**
HMII Risk Score (27)	HMII	**Age**, Center volume	--	**Albumin**, **Creatinine**, **INR**
Revised HMRS (28)	HMII HVAD	**Age**	--	**Albumin**, **Creatinine**, **INR**
MELD (36)	XVE HMII	--	--	Sodium, **Creatinine**, **Bilirubin**, **INR**

MELDxi (31)	HMII HVAD	--	--	Sodium, **Creatinine,** **Bilirubin**
Bayesian Model* (32)	HMII HVAD	Previous cardiac surgery, Destination Therapy, INTERMACS profile, ECMO, Dialysis, **intubation**		Hemoglobin, **Creatinine,** prealbumin, **INR**
Right Heart Failure Prediction Models				
Michigan Risk Score (35)		**Use of vasopressor support**	none	**AST ≥80 IU/L,** **Bilirubin ≥2.0 mg/dL,** **Cr ≥2.3 mg/dL**
CRITT Score (30)	Pulsatile (1st generation) pumps	RV function by echo, Severe tricuspid	CVP >15	--

		insufficiency, **Intubation**, Tachycardia		
Kormos Score (33)	HMII	**Intubation**	RA:WP >0.63	**BUN >39**
EUROMACS-RHF (37)		Severe RVF by echo, **use of ≥3 inopressors**, INTERMACS Profile 1-3	RA:WP >0.54	Hg ≤10

Common variables across models are highlighted by color. *AST*, aspartate aminotransferase; *BMI*, body mass index; *BUN*, blood urea nitrogen; *DTRS*, Destination Therapy Risk Score; *ECMO*, extracorporeal membrane oxygenation; *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support; *RVF*, severe right ventricular failure. *Bayesian models included many risk factors entered for each patient. The variables listed are those common to most models studied for mortality after LVAD at various time points

inability to tolerate stressors leading to a progressive loss of physiologic functions [44]. In the advanced HF population, it is critical to categorize frailty in two ways: reversible frailty that is a result of end-stage HF that will improve with initiation of MCS versus irreversible frailty that is recalcitrant to advanced HF interventions. Two recent studies assessing the Fried Score, a commonly used measure of frailty, found poor association between assessed frailty and clinical outcomes after LVAD implantation [42, 45]. Cooper et al. [42] performed a large retrospective analysis of patients implanted for the destination therapy indication in INTERMACS and found that when components of the Fried Score were added to a generic provider assessment of frailty (Is patient frail?: yes/no), there was a weak association between patients who were defined as frail and LVAD hospitalization lengths of stay, 1-year mortality, infection, and/or rehospitalization. A smaller prospective study by Joseph et al. [45] used an adjusted Fried Score (integrating the components of exhaustion, weak grip strength, and patient reported activity level), demonstrating correlations between the adjusted Fried Score and inpatient death, extended lengths of stay, and delayed extubation. The findings remained significant after adjusting for patient age, sex, and MELD score, suggesting that these three variables may be more predictive of reversible frailty. Finally, the impact of living on LVAD support (which presently entails having a cord called a driveline that attaches outside the body to a device controller and batteries) and LVAD-related complications (bleeding, stroke) on QoL is critical for defining LVAD "success." Kiernan et al. [46] examined preoperative Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure (MLWHF) score in patients undergoing LVAD support, finding that low preoperative QoL and functional capacity metrics along with multimorbidity (including diabetes and lung disease) were predictive of a patient's failure to clinically improve after LVAD (lack of improved FC and QoL metrics) and identified patients at increased risk of death after LVAD. In a study of patients enrolled into the HeartMate 3 (Abbott, Abbot Park, IL) clinical trial, a disconnect was found between the occurrence of LVAD complications and KCCQ and MLWHF scores such that the scores failed to worsen in those with serious LVAD complications [45]. Clearly, more research is needed to better characterize quality of life after VAD and the impact of LVAD-related complications on such.

Conclusions

The field of advanced heart failure has extensively evolved over the last decade, providing carefully selected patients with

advanced systolic HF improved survival and quality of life with LVAD and/or cardiac transplant. Early referral, prior to the onset of end-organ dysfunction or hemodynamic instability, is critical to achieving good outcomes after LVAD/transplant and is integral to the shared decision-making process that occurs between providers and patients during the discussion of advanced HF therapy options, risks, and benefits. Survival and morbidity have improved with each generation of LVAD technology and we can anticipate that these gains will lower referral thresholds for device implant, allowing a less ill HF subpopulation for consideration. Thus, it is imperative that clinicians collaborate within and between health systems to ensure patients with severe HF are offered all appropriate options.

Compliance with Ethical Standards

Conflict of Interest Dr. Michaels declares no conflict of interest. Dr. Cowger is a paid speaker and consultant for Abbott and Medtronic, manufacturers of the HeartMate and HVAD products, respectively. Henry Ford receives clinical trial research funding from Abbott and Medtronic.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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