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Identifying Stage D Heart Failure: Data From the Most Recent Registries

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Abstract

Purpose of Review Improving outcomes with durable mechanical circulatory support have led to expanding interest in the earlier recognition of patients destined to develop refractory heart failure (HF). The recognition of advanced HF has received increasing attention.

Recent Findings The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry developed patient profiles of advanced HF to describe the spectrum of patients with refractory HF undergoing mechanical circulatory support. These patient profiles have been extended to advanced HF patients on medical therapy and used to align outcomes with medical and device therapy in the Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS) registries and the ROADMAP study.

Summary Shared decision-making about treatment options for advanced HF requires individualized consideration of risks and benefits beyond survival. Future studies, including the ongoing Registry for Vital Information for VADs in Ambulatory Life (REVIVAL) study, will provide prognostic information for patients transitioning from stage C to stage D HF to help patients, caregivers, and physicians navigate the increasingly complex terrain of HF care.

Keywords Heart failure · Mechanical circulatory support · Registries · Ventricular assist device · Prognosis

Introduction

The prevalence of heart failure (HF) continues to rise with recent estimates suggesting 6.5 million American adults are living with HF [1]. By 2030, more than 8 million adults are projected to have HF with an annual cost of almost 70 billion dollars [2]. Over the last 50 years, medical and electrical therapies improved and mortality from HF dramatically reduced, although the 5-year mortality following initial diagnosis remains greater than 40% [3–5]. Options for advanced surgical therapies are available to select patients with HF. Heart transplant listings have steadily increased with a 127% 10-year increase in 2016 compared with 2006 with 3209 adult heart transplants being performed in 2016 [6]. Unrestricted by a limited donor supply, mechanical circulatory support (MCS) device implantation has seen even greater expansion, now exceeding 2500 per year [7], up from under 100 just over 10 years ago [8]. Adding to the enthusiasm for these advanced therapies, survival rates have continued to increase, with modern 1 year survival for MCS recipients > 80% [7] and for heart transplant recipients > 90% [6].

There is a critical need to identify patients with refractory HF who may benefit from these advanced surgical therapies. The optimal method for identifying eligible patients has been slowly evolving, with thresholds for considering MCS moving to earlier stages of HF as outcomes following MCS have improved. While pivotal clinical trials have propelled innovative next-generation devices to regulatory approval [9], prospective registries remain essential to monitoring how to best implement these therapeutic advancements. We will review the lessons learned about stage D HF from recent medical

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and device registries, with a focus on the expanding interest in identifying those patients still ambulatory on oral therapies who may merit consideration of MCS.

What Is Stage D HF?

In the most recent ACCF/AHA HF guidelines, HF is recognized as a progressive disease with identifiable stages at which different treatments are recommended to reduce morbidity and mortality [10]. Stage D heart failure has been called many names over the years including "end-stage" and "refractory" HF [11, 12]. For the purposes of this review, all these terms are used interchangeably. Stage D HF typically describes patients who experience persistent symptoms despite optimal guideline-directed medical therapy (GDMT) who may be eligible for advanced therapies [10].

Given the potential implications of identifying stage D HF, a number of more precise definitions have been proposed which can be integrated into clinical care including those by the Heart Failure Society of America [11], the European Society of Cardiology [12], and the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) [10] **(**Table 1**).** Updates in these guidelines reflect the rapidly changing landscape of HF patients as well as available therapies. Compared with prior guidelines, there is a recognition of the need to be on GDMT which includes implantable electrical devices, the changing locations of care with options for outpatient intravenous diuretics, the inclusion of intractable arrhythmias as a marker of stage D, and emphasis on confirmation that HF is responsible for symptoms. Delineating the specific role HF plays in overall symptom burden has become increasingly necessary given the advancing age and comorbid complexity of contemporary patients with HF [13]. Importantly, current definitions of stage D HF do not require a reduced left ventricular ejection fraction, given the recognition of similar disease burden, morbidity, and mortality in patients with HF with preserved ejection fraction [14].

Presently, stage D patients with HF and reduced ejection fraction are still those most likely to be considered for advanced therapies including intravenous inotropes, MCS placement, and transplantation. Despite improvements in the treatment of HF, an estimated 1–10% of patients with HF progress to stage D each year [15, 16]. Among this group, prognosis without advanced therapies from clinical trials of systolic HF is dismal with only 11–25% survival at 1 year [11, 17, 18]. Complicating this, the perception of prognosis among both treating physicians and patients may be inaccurate. Less than half of physicians accurately predicted survival among HF patients, including overestimation of survival by cardiologists [19, 20]. Given the current prognosis and the discordance between both physician and patient perception of prognosis, identification of stage D HF patients is critical not only to allow the receipt of information about and the acceptance of advanced therapies but also to enable patients and their families to participate in advanced care planning.

Identification of Advanced Heart Failure

Historically, advanced HF has been identified through a combination of symptoms, individual predictors, risk scores, functional parameters, and clinical events [11]. In a review of criteria used to identify patients with advanced HF in 134 clinical trials, the most common criteria were New York Heart Association (NYHA) functional class (*n*, %; 119, 88.8%), left ventricular ejection fraction (LVEF) (84, 62.7%), specific HF symptoms present (18, 13.4%), inotrope dependence (17, 12.7%), prior HF admission (14, 10.4%), peak oxygen consumption (14, 10.4%), and cardiac index (14, 10.4%) [21]. While NYHA functional class is the most consistently used measure, there remains considerable variation among practitioners in assessing class, and assignment of NYHA class remains largely dependent on a given patient's desired level of activity [22]. Furthermore, many of the symptoms of HF are fairly non-specific, with overlap with comorbidities and frailty which is increasingly recognized in this population [23].

HF Taxonomy: Classes, Stages, and Profiles

The modern evolution of classifications for severity of disease has been influenced by the available therapeutic options. When transplantation was the only approved therapy for stage D HF, the persistence of NYHA class IV symptoms at rest or minimal exertion was adequate to define stage D HF. As the benefits of durable MCS devices extended into prolonged support outside of the hospital, they began to be considered for prevention as well as treatment of terminal hemodynamic decompensation leading to secondary organ dysfunction. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), the landmark US Registry of approved durable MCS devices, developed a new classification scheme for advanced HF **(**Fig. 1**).** In the wake of the REMATCH trial that expanded the MCS indication to include lifelong destination therapy, part of the INTERMACS mission was to distinguish patients with various levels of compromise to standardize comparison of outcomes for different devices, different patients, and different implanting centers.

The INTERMACS profiles were created to describe patients failing medical therapy who would benefit from advanced therapies beyond the NYHA classifications with inclusion of arrhythmia burden, the need for temporary support, and recurrent hospitalizations as modifiers [24, 25]. The colloquial descriptor of "crash and burn" for profile 1 described the patient on maximal inotropic support in whom survival was defined in hours.

Table 1 Recent major society definitions of advanced heart failure

2018 HFA of the ESC[a]	2015 HFSA[b]	2013 ACCF/AHA[c]
All of the following must be present despite GDMT: 1. Severe and persistent symptoms of heart failure 2. Severe cardiac dysfunction including one of the following: (a) LVEF ≤ 30% (b) Isolated RV failure (c) Non-operable severe valve abnormalities (d) Congenital abnormalities (e) Persistently high BNP or NT-proBNP and severe diastolic dysfunction or LV structural abnormalities 3. Episodes of the following prompting an unplanned visit or hospitalization in the past 12 months: (a) Volume overload requiring high-dose diuretics (b) Low cardiac output necessitating inotrope or vasoactive drugs (c) Malignant arrhythmias 4. Severe exercise capacity limitation with inability to exercise or low 6MWD or pVO2 thought to be secondary to HF	1. Presence of progressive and/or persistent severe signs and symptoms of HF despite GDMT. 2. Generally accompanied by (a) frequent hospitalization, (b) severely limited exercise tolerance, and (c) poor quality of life and is associated with high morbidity and mortality. 3. The HF syndrome is the primary reason for the progressive decline.	1. Persistent severe symptoms despite maximum GDMT. 2. Presence of events and/or findings useful for identifying: (a) Repeated (≥ 2) hospitalizations or ED visits for HF in the past year (b) Progressive deterioration in renal function (c) Weight loss without other cause (d) Intolerance to ACE inhibitors due to hypotension and/or worsening renal function (e) Intolerance to beta blockers due to worsening HF or hypotension (f) Frequent systolic blood pressure < 90 mmHg (g) Persistent dyspnea with dressing or bathing requiring rest (h) Inability to walk 1 block on the level ground due to dyspnea or fatigue (i) Escalating diuretic dosing and/or use of supplemental metolazone therapy (j) Progressive decline in serum sodium (k) Frequent ICD shocks

HFA, Heart Failure Association; *ESC*, European Society of Cardiology; *HFSA*, Heart Failure Society of America; *ACCF*, American College of Cardiology Foundation; *AHA*, American Heart Association; *GDMT*, guideline-directed medical therapy; *LVEF*, left ventricular ejection fraction; *RV*, right ventricular; *BNP*, B-type natriuretic peptide; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *LV*, left ventricular; *6MWD*, 6-min walk distance; pVO_2, peak oxygen consumption; *HF*, heart failure; *ACE*, angiotensin-converting enzyme; *ICD*, implantable cardioverter defibrillator

[a] Crespo-Leiro et al. [12]

[b] Fang et al. [11]

[c] Yancy et al. [10]

Profile 3 was defined as "stable on inotropes," which could be either in or out of the hospital, recognizing regional variation in availability of inotropic infusions at home. "Resting symptoms" daily despite high doses of diuretic therapy without any intravenous medications defined profile 4, which was essentially chronic NYHA class IV symptoms. The designations of "homebound" but comfortable at rest defined profile 5, and "walking wounded" with limited activity outside the home defined profiles 6 and 7. The least compromise was in profile 7, which was added as a placeholder for patients comfortable with some limitation, without frequent exacerbations. The INTERMACS patient profiles have been shown to more accurately predict failure of medical therapy and mortality than the NYHA classification [26]. Despite emerging utility of this powerful shorthand descriptor of stage D patients, the INTERMACS profiles have not been used as primary entry criteria in clinical studies. Rather entry criteria have been designed to enrich cohorts with specific patient profiles.

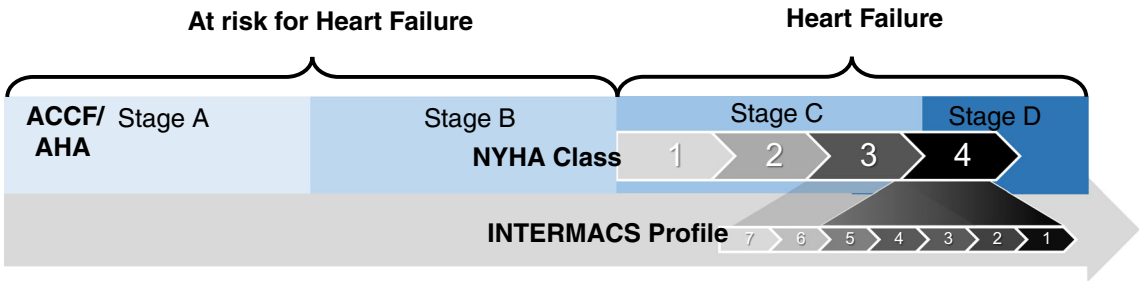

Fig. 1 Classification schemes for heart failure severity. Overlapping classification systems provide complementary descriptive and prognostic information for patients with advanced heart disease. The New York Heart Association (NYHA) classifies dynamic functional limitation and the American Heart Association (AHA)/American College of Cardiology (ACC)-Stages of Heart Failure highlight antecedent risk factors and disease progression, while the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) patient profiles integrate symptom burden and ongoing measures use to treat evolving shock

Aligning Medical and Device Outcomes

There are clear benefits for MCS implantation among eligible patients in profiles 1–2 compared with medical therapy [17, 27]. Ambulatory patients in profile 3 receiving continuous inotropic support have improving survival but still only 50% per year, well below that offered by contemporary CF-LVAD therapy [28]. As a result, dependence on intravenous inotropic support as in INTERMACS profile 3 has traditionally been considered the threshold that defines irreversible advanced HF and mandates consideration of advanced therapies. In the absence of this clear marker of severity, identifying which patients with advanced HF on oral therapies (INTERMACS profiles 4–7) who would likely benefit from MCS becomes challenging. The largest potential impact of MCS on public health is for patients on oral HF therapies, well before the development of circulatory shock and end-organ dysfunction, in whom support could be employed electively for long-term benefit with diminished perioperative risk. However, in 2015–2016, only 13% of device implants in INTERMACS were performed in patients prior to inotrope dependence [7]. In this ambulatory population, for whom death from HF is not imminent, shared decision-making about MCS requires more measured and individualized consideration of risks and benefits beyond survival.

Integral to the original intent of INTERMACS was comparison between patients receiving approved LVADs and ambulatory patients living with advanced HF who were not receiving MCS. Until recently, the field has struggled to identify ambulatory patients who are both sick enough (with regard to cardiac dysfunction and limitations) and healthy enough (with regard to non-cardiac issues) to derive more benefit from MCS than from contemporary oral medical therapy. Creating a contemporary medical therapy comparison group became necessary to understanding stage D HF with the goal of better identifying patients failing medical therapy who would benefit from advanced therapies.

MedaMACS Screening Pilot

The Medical Arm of Mechanically Assisted Circulatory Support, or MedaMACS, was a prospective cohort study designed to increase our understanding of HF trajectory among patients with advanced symptoms on oral therapies. MedaMACS was completed in two phases, an initial pilot study that enrolled 168 non-inotrope-dependent patients between 2010 and 11 who were being followed at VAD centers, followed by a pilot study of 162 non-inotrope-dependent patients from 11 centers in 2013–2015 with data fields designed to align with those of INTERMACS **(**Table 2**).** Among screening pilot participants, over half were INTERMACS profile 4 or 5 (23% profile 4, 32% profile 5, and 45% profile 6/7). Despite being less sick, over half of the patients were somewhat or definitely willing to consider MCS based on their current condition. As INTERMACS profile decreased, more patients were definitely willing to consider MCS, including 35% of participants in INTERMACS profile 4. Importantly, patients equally valued the potential impact of MCS therapy on both quality of life and mortality [29•]. The pilot study additionally provided insight into the use of INTERMACS profiles for risk assessment in ambulatory HF patients not being considered for MCS. In the screening study, less than half of the cohort remained alive on medical therapy without advanced therapies (LVAD or transplant). At 1 year, just 39% of INTERMACS profile 4 patients were alive without receiving advanced therapies compared with 84% of profile 6/7 patients. A number of important differences were identified that differentiated the higher profile groups including increased tolerance of neurohormonal antagonists and less hospitalizations [30]. INTERMACS profiles were also associated with HRQOL and health utility as expected with both worse in lower profiles [31••].

MedaMACS Study

The MedaMACS pilot study built on the screening study but enrolled predominantly outpatients in profiles 5–7. Among

Table 2 Clinical studies of ambulatory patients with advanced heart failure. Revised and used with permission from Springer Nature

	MedaMACS screening pilot	ROADMAP	MedaMACS study	REVIVAL
Number of Patients	166	103 on OMM (200 total)	161	400
Enrollment Period	2010–2011	2011–2013	2013–2015	2015–2016
Inclusion criteria				
NYHA class	III–IV	IIIB/IV	III–IV	II–IV
EF	≤ 30%	≤ 30%	≤ 35%	≤ 35%
High-risk features	2 HF hosp in 12 months or 1 HF hosp + 1 high-risk feature: peak VO_2 < 16 ml/kg/min for men, peak VO_2 < 14 ml/kg/min for women w/ RER > 1.08 or < 55% predicted, or 6MW < 300 m, or BNP > 800 ng/ml, or serum Na^+ < 135 mEq/dl	≥ 1 HF hosp in 12 months or 2 unscheduled EW visits for HF and 6MW < 300 m	1 HF hosp in 12 months and 1 high-risk feature: additional HF hosp in 12 months or peak VO_2 < 16 ml/kg/min for men, peak VO_2 < 14 ml/kg/min for women, 6MW < 300 m, or outpatient NT-BNP > 4000 ng/dl, or SHFM 1 year predicted survival ≤ 83%	2 HF hosp in 12 months, or 1 HF hosp in 12 months with outpt BNP ≥ 500 pg/ml or NT-proBNP ≥ 2000 pg/ml, or if no HF hosp, ≥ 1 high-risk feature: peak VO_2 ≤ 16 ml/kg/min or ≤ 55% predicted with RER ≥ 1.05, or 6MW ≤ 350 m, or BNP ≥ 750 pg/ml or NT-proBNP ≥ 3000 pg/ml as outpt (w/o HF hosp), SHFM 1 year predicted survival ≤ 85%
Exclusion Criteria	Intravenous inotropes Listed for transplant	Intravenous inotropes Listed for transplant DT VAD ineligible	Intravenous inotropes Listed for transplant Congenital heart defect Amyloidosis	Intravenous inotropes Listed UNOS 1A/B for transplant Congenital heart defect Amyloidosis Dialysis or serum Cr > 3 mg/dl
INTERMACS profiles enrolled	4–22% 5–32% 6–34% 7–12%	4–34% 5–28% 6–34% 7–2%	4–12% 5–32% 6–49% 7–7%	4–8% 5–21% 6–39% 7–32%
Major findings	• INTERMACS profiles identify high-risk patients on medical therapy • Profile 4 patients had 52% survival without LVAD by 6 months and 39% at 1 year • Most participants would be willing to consider LVAD and place considerable emphasis on anticipated improvement in QoL	• Survival with improved functional (6MW > 75 m) status better on HMII than OMM at both 1 and 2 years • Patients choosing LVAD more likely to be in sicker INTERMACS profile and have poorer QoL • Intent-to-treat survival had no difference between LVAD and OMM at 1 year	• High early event rates in patients with questionable eligibility for VAD/Tx • Physicians identified patients to be at higher risk than patients themselves • Compared with contemporary device registrants in INTERMACS, survival on LVAD improved in profiles 4–5 compared with medical therapy	• Overall event rate 24% in this predominantly profile 5–7 cohort • Positioned to map transition from stage C to stage D HF • Core labs for exercise, echocardiography, and biomarkers will facilitate deeper phenotyping of patients at risk for refractory HF

BNP, B-type natriuretic peptide; *Cr*, creatinine; *DT*, destination therapy; *EF*, ejection fraction; *EW*, emergency ward; *HF*, heart failure; *HMII*, HeartMate II assist device; *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support; *MedaMACS*, Medical Arm for Mechanically Assisted Circulatory Support; Na^+, sodium; *NYHA*, New York Heart Association; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *OMM*, optimal medical management; *QoL*, quality of life; *REVIVAL*, Registry Evaluation of Vital Information for VADs in Ambulatory Life; *ROADMAP*, Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients; *SHFM*, Seattle Heart Failure Model; *Tx*, transplant; *UNOS*, United Network of Organ Sharing; *VAD*, ventricular assist device; VO_2, oxygen consumption; *6MW*, 6-min walk

the 162 patients, 12% were profile 4, 32% were profile 5, 49% were profile 6, and 7% were profile 7. By 2 years, almost half (47%) had required advanced therapies or died including 11% receiving LVAD support and 12% receiving transplant. When patients in MedaMACS were compared with 1752 contemporary continuous flow LVAD recipients in INTERMACS (dates of implant), survival with LVAD therapy was improved compared with medical therapy for profiles 4 and 5 [32]. In a subset of these patients who were ineligible for either destination therapy (DT) LVAD or transplant, mortality was higher compared with patients eligible for either DT-LVAD or transplant (23.3% vs 8% in the DT-LVAD group and 5.9% in the

transplant group; $p = 0.02$). The reasons for ineligibility were multiple including advanced age, renal dysfunction, malnutrition, pulmonary hypertension, frailty, limited social support, and non-compliance [33]. These findings from the MedaMACS pilot highlight that not only do ambulatory INTERMACS profile 4–7 participants have high event rates, but also there is a need to begin having discussions about preferences for therapies before progressive end-organ dysfunction leaves the patient ineligible for therapies, as this portends a worse prognosis [32, 33].

Another goal of MedaMACS was to understand how perception of prognosis translates into informed decision-making for physicians and patients. The MedaMACS pilot study assessed the current state of both physician and patient understanding of prognosis with a survey about short-term risk for requiring advanced therapy with a median follow-up of 13 months. Of the 161 patients completing the survey, 86% of patients with ambulatory advanced HF thought that they were low risk for an event in the next year, yet 69% of the same patients were identified by their treating physicians as high risk. At 1 year, 38% of patients registered had experienced an endpoint [34••]. Neither physician nor patient predictions accurately identified high-risk patients, highlighting the difficulty of identifying stage D patients in clinical practice even among experienced HF clinicians and the need for improved metrics of assessment. At the very least, recognition of those likely to fail medical therapy will hopefully enable discussions on patient preferences for care in ambulatory patients with HF.

Our ability to have timely discussions remains limited by difficulties in understanding prognosis and identifying stage D patients. Despite being at centers with experience providing advanced therapies, only 24% of participants in MedaMACS had undergone formal evaluation for LVAD or transplant. While some patients may have developed obvious contraindications to these advanced therapies and others were truly too well, prior work suggests inaccurate patient and physician understanding of prognosis and trajectory likely contributory [34••]. Shared decision-making remains the emphasis in deciding appropriate therapies for stage D HF patients [10]. MedaMACS illuminated several important limitations in our ability to engage effectively in shared decision-making with stage D HF patients related to disease trajectory and overly optimistic prognostic expectations.

ROADMAP

The Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) trial looked to improve our current understanding and identification of ambulatory stage D patients through prospective, observational comparison of medical therapy versus durable MCS support in ambulatory patients less sick than MedaMACS (Table 2). The goal of the study was to enroll patients with a 20–30% 1-year mortality. In addition to low ejection fraction, patients had to be on stable GDMT with persistent NYHA class IIIb or IV symptoms, ineligible for transplant, and have either 1 HF hospitalization or 2 unscheduled emergency room or infusion clinic visits in the past 12 months and a 6-min walk distance (6MWD) less than 300 m. Participants chose either continued GDMT or DT-LVAD at the time of enrollment in the study. The primary endpoint was a composite of survival and improvement in 6MWD ≥75 m [35].

Being an observational study, there were several important differences between the DT-LVAD patients ($n = 97$) and the medical therapy patients ($n = 103$) at baseline. The LVAD patients had lower QOL and were sicker based on INTERMACS profiles, NYHA functional class, and Seattle HF Model (SHFM) predicted survival [36]. The patients enrolled in the study were high risk. Over half in each arm required hospitalization during the 2-year study period (80% LVAD and 62% medical therapy). At 2 years, more participants in the LVAD group met the combined endpoint of survival with improved 6MWD (30% vs 12%; odds ratio, 95% confidence interval, 3.2, 1.3–7.7). There was no difference for survival in the intention-to-treat analysis (22%, $n = 23$ of the medical therapy arm received delayed LVAD) but there was a 30% improvement in survival (70% vs 41%, $p < 0.001$) when analyzed as treated [37]. There was an initial increase in adverse events driven by bleeding in the LVAD group at 1 year [36].

There are several additional observations from ROADMAP that warrant discussion when attempting to identify stage D HF. Given the prominent role of risk scores to aid in identification of high-risk patients, the investigators explored the accuracy of the SHFM in the medical therapy arm. Among the 103 participants on medical therapy, the SHFM predicted survival (ROC area under curve = 0.71; 95% CI 0.59–0.83; p value < 0.001) but overestimated LVAD free survival (ROC area under curve = 0.56, 95% CI 0.44–0.68; p value > 0.20) at 1 year. The Heartmate II Risk Score (HMRS) performed less well and did not discriminate events at 1 year (ROC = 0.62, 95% CI 0.47–0.76; p value > 0.12) [38•]. Taken together, while the SHFM predicted 1-year mortality, neither risk score adequately differentiated non-inotrope-dependent patients who would clinically worsen. The ROADMAP investigators also looked at the outcomes of the medically managed participants grouped by INTERMACS profiles [24]. Of the medically managed patients, 35% ($n = 35$) were profile 4 and 66% ($n = 66$) were profiles 5–7. Compared with medical therapy, INTERMACS profile 4 participants who underwent LVAD were more likely to meet the composite primary endpoint (survival with improved 6MWD) at 1 year (40% vs 15%; odds ratio = 3.9 (1.2–12.7)). There was, however, no difference for INTERMACS profile 5–7 patients. Findings were similar

for the composite endpoint of survival on original therapy with acceptable health-related quality of life (defined as VAS score ≥ 60) [39]. In summary, current risk scores do not adequately predict who will clinically worsen, and there did not appear to be a clear advantage for LVAD in medically managed INTERMACS profile 5–7 patients with respect to either improvement in HRQOL or survival.

REVIVAL: Mapping the Transition From Stage C to Stage D

Current use of LVADs for treatment of refractory stage D heart failure continues to grow with greater than 22,000 implanted over 10 years [7]. Given the poor HRQOL among ambulatory patients with advanced HF, consideration has been given to earlier implant among less symptomatic ambulatory patients with by INTERMACS profile 5–7 symptoms. Greater understanding of not only prognosis in this less sick group but also factors that drive patient choice for LVAD therapy in this group is critical as our understanding of the heterogeneity of potential benefit remains unclear, and the decision is certainly preference sensitive. In 2015–2016, of the 5400 registered implants in INTERMACS, only 1.6% were in patients with profiles 5–7 at the time of LVAD implantation [7]. Much of this reluctance stems from the unacceptably high adverse event rates across approved and investigational devices. Additional expansion of LVADs into ambulatory patients in INTERMACS profile 5–7 HF will require not just improved technology with fewer adverse events but also better prognostic tools to identify those at greatest risk of dying without MCS and those who are most likely to have favorable outcome with VAD support.

Recent attention to adverse events on LVAD therapy—particularly to pump thrombosis and stroke—prevented equipoise for randomizing patients in NYHA class III to medical versus currently approved device therapy [40]. The closing of the REVIVE-IT (Randomized Evaluation of VAD Intervention before Inotropic Therapy) deprived the HF community of important information on a medically managed cohort in parallel to device therapy. Fortunately, the prospective registry intended to be part of the REVIVE-IT effort has been reformulated as the Registry Evaluation of Vital Information for VADs in Ambulatory Life (REVIVAL). REVIVAL is a prospective, observational multicenter patient cohort that has completed enrollment and follow-up of 400 patients with ambulatory advanced HF across 21 sites in the USA. Unlike MedaMACS, REVIVAL also includes patients listed for transplant as status 2 (former United Network of Organ Sharing Status definitions). This group was included as transplant candidates on oral medical therapy alone face a growing waitlist and difficult decisions about when and if to pursue MCS. Entry criteria were designed to map the transition from stage C to stage D HF. Overall 92% of enrollees were in INTERMACS profiles 5–7, and the 1-year combined rate of urgent transplant, death, or durable MCS was 24% [41]. To better phenotype patients with advancing HF, REVIVAL enrolled more patients than both phases of MedaMACS combined and nearly four times as many ambulatory advanced HF patients on optimal medical therapy than ROADMAP **(**Table 2**).**

The REVIVAL cohort recently completed 2-year follow-up for death, durable MCS, or transplantation. Each available participant also contributed data 2 months following enrollment to core laboratories on cardiopulmonary exercise testing, echocardiography, and biomarkers. Indices of functional capacity, frailty, and quality of life, as well as caregiver burden, were assessed serially to better understand the factors underpinning the decision to proceed with MCS. By providing detailed information on patient-reported outcomes, prognosis, and dynamic clinical trajectories through serial evaluation, REVIVAL will determine the feasibility of identifying candidates for a trial of next-generation LVAD technology and other investigational therapies in NYHA class III HF.

Remaining Challenges and Future Directions

Despite new insights from medical registries, the available evidence suggests that predicting which patient with HF will fail medical therapy remains challenging. There are a number of high-risk features identified in recent HFSA guidelines that are highly suggestive of stage D HF and should trigger a referral to a HF specialist [11]. Assessment requires using a holistic evaluation of a patient and not placing undo emphasis on one finding. Using a combination of history (e.g., hospitalizations, functional class), objective exercise capacity testing (e.g., 6MWT, maximal cardiopulmonary exercise testing), therapy review (e.g., lack of response to diuretics, inability to tolerate angiotensin-converting enzyme inhibitors, ARBs, or beta blockers), laboratory data (e.g., serum sodium and creatinine), and risk prediction score (e.g., SHFM), one can facilitate timely referral to an advanced HF specialist for assessment of HF status. Unfortunately, until available predictive assessment improves, stage D HF largely remains a diagnosis of "knowing it when you see it." Moreover, a major ongoing limitation has been the focus on current symptoms and risk markers of refractoriness rather than the trajectory of illness, which can be dynamic and unpredictable in a given patient [11, 42].

Our understanding of the transition to and management of stage D HF is even more limited in several growing patient populations. Elderly patients have thus far not been enrolled in the prospective cohort studies including MEDAMACS, ROADMAP, and REVIVAL [32, 35, 43]. Current evidence suggests that advancing age is consistently associated with

worse outcomes [11, 44] and more limited availability of advanced therapies [45]. Several comorbidities that further destabilize the patient with advanced HF and impact what optimal medical therapy may look like are emerging [11]. Frailty is a syndrome of decreased physiologic reserve and increased vulnerability to stress [46]. Occurring more commonly in the elderly, frailty has been consistently linked to increased morbidity and mortality in advanced HF patients [46]. REVIVAL looks to give insight in the impact of frailty on risk prediction and outcomes with ascertainment of commonly used measures of frailty. Depression similarly has been associated with consistently worse outcomes including patient-reported outcomes such as HRQOL [47] and usual measures of morbidity and mortality [48, 49]. Although current definitions for stage D HF do not take LVEF into consideration [10–12], current evidence-based therapies that improve outcomes for patients with preserved LVEF are limited [50]. Despite this, identification of a patient with stage D advanced HF remains critically important to ensure development of an individualized treatment plan, including advanced care planning. While ideally conversations about advanced care planning occur prior to the transition to stage D HF [11], the results of the Palliative Care in Heart Failure (PAL-HF), which included participants with varied EF, suggests that an interdisciplinary approach to the stage D patient including palliative care can have a positive impact on important patient-centered outcomes including QOL, anxiety, depression, and spiritual well-being [51].

A significant challenge remains in how to best engage in shared decision-making and how to translate registry findings into shared decision tools. One such undertaking was the recent Effectiveness of an Intervention Supporting Shared Decision-Making for Destination Therapy Left Ventricular Assist Device (DECIDE-LVAD) trial. In the trial, an intervention supporting shared decision-making was associated with improved patient decision quality as measured by higher concordance between stated values and patient-reported treatment choice [52]. Incorporation of registry data into ongoing improvements in shared decision-making tools, particularly by aligning anticipated outcomes with medical and device therapy, will better enable patients to make the optimal decision aligned with their values and preferences.

Conclusions

Increasing therapeutic options for the management of advanced HF have made early recognition of stage D HF critical. Recent registry and cohort studies have greatly contributed to our understanding of advanced HF and given insight into outcomes with the use of modern therapies. Ongoing work is aimed at identifying patients at greatest risk for the transition from stage C to stage D HF to better enable advanced care planning and inform shared decision-making around advanced therapies.

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Compliance With Ethical Standards

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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.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation. 2018;137(12):e67–e492.
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6(3):606–19.
3. Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. Circulation. 2006;113(6):799–805.
4. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol. 2008;101(7):1016–22.
5. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, et al. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years. Eur J Heart Fail. 2014;16(3):317–24.
6. Colvin M, Smith JM, Hadley N, et al. OPTN/SRTR 2016 annual data report: heart. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2018;18(Suppl 1):291–362.
7. Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. J Heart Lung Transplant : Off Publ Int Soc Heart Transplant. 2017;36(10):1080–6.
8. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant : Off Publ Int Soc Heart Transplant. 2015;34(12):1495–504.
9. Mehra MR, Goldstein DJ, Uriel N, Cleveland JC Jr, Yuzefpolskaya M, Salerno C, et al. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. N Engl J Med. 2018;378(15):1386–95.
10. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association

Task Force on practice guidelines. Circulation. 2013;128(16):e240–327.
11. Fang JC, Ewald GA, Allen LA, Butler J, Westlake Canary CA, Colvin-Adams M, et al. Advanced (stage D) heart failure: a statement from the Heart Failure Society of America Guidelines Committee. J Card Fail. 2015;21(6):519–34.
12. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20:1505–35.
13. Ahluwalia SC, Gross CP, Chaudhry SI, Leo-Summers L, Van Ness PH, Fried TR. Change in comorbidity prevalence with advancing age among persons with heart failure. J Gen Intern Med. 2011;26(10):1145–51.
14. Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Current heart failure reports. 2013;10(4):401–10.
15. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC Jr, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. Circulation. 2007;115(12):1563–70.
16. Xanthakis V, Enserro DM, Larson MG, Wollert KC, Januzzi JL, Levy D, et al. Prevalence, Neurohormonal correlates, and prognosis of heart failure stages in the community. JACC Heart Fail. 2016;4(10):808–15.
17. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435–43.
18. Rogers JG, Butler J, Lansman SL, Gass A, Portner PM, Pasque MK, et al. Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTrEPID trial. J Am Coll Cardiol. 2007;50(8):741–7.
19. Warraich HJ, Allen LA, Mukamal KJ, Ship A, Kociol RD. Accuracy of physician prognosis in heart failure and lung cancer: comparison between physician estimates and model predicted survival. Palliat Med. 2016;30(7):684–9.
20. Allen LA, Yager JE, Funk MJ, Levy WC, Tulsky JA, Bowers MT, et al. Discordance between patient-predicted and model-predicted life expectancy among ambulatory patients with heart failure. JAMA. 2008;299(21):2533–42.
21. Bjork JB, Alton KK, Georgiopoulou VV, Butler J, Kalogeropoulos AP. Defining advanced heart failure: a systematic review of criteria used in clinical trials. J Card Fail. 2016;22(7):569–77.
22. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart. 2007;93(4):476–82.
23. Murad K, Kitzman DW. Frailty and multiple comorbidities in the elderly patient with heart failure: implications for management. Heart Fail Rev. 2012;17(4–5):581–8.
24. Stevenson LW, Pagani FD, Young JB, Jessup M, Miller L, Kormos RL, et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant. 2009;28(6):535–41.
25. Stewart GC, Stevenson LW. INTERMACS and MedaMACS: how will they guide future therapy? Curr Cardiol Rep. 2013;15(9):394.
26. Samman-Tahhan A, Hedley JS, McCue AA, Bjork JB, Georgiopoulou VV, Morris AA, et al. INTERMACS profiles and outcomes among non–inotrope-dependent outpatients with heart failure and reduced ejection fraction. JACC: Heart Failure. 2018;6(9):743–53.
27. Stevenson LW, Miller LW, Desvigne-Nickens P, Ascheim DD, Parides MK, Renlund DG, et al. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). Circulation. 2004;110(8):975–81.
28. Hashim T, Sanam K, Revilla-Martinez M, Morgan CJ, Tallaj JA, Pamboukian SV, et al. Clinical characteristics and outcomes of intravenous inotropic therapy in advanced heart failure. Circ Heart Fail. 2015;8(5):880–6.
29.• Stewart GC, Kittleson MM, Cowger JA, Johnson FL, Patel CB, Mountis MM, et al. Who wants a left ventricular assist device for ambulatory heart failure? Early insights from the MEDAMACS screening pilot. J Heart Lung Transplant. 2015;34(12):1630–3. **Ambulatory advanced heart failure patients equally value the impact of MCS therapy on both quality of life and mortality.**
30. Stewart GC, Ambardekar AV, Kittleson MM. Defining ambulatory advanced heart failure: MedaMACS and beyond. Current heart failure reports. 2017;14(6):498–506.
31.•• Stewart GC, Kittleson MM, Patel PC, Cowger JA, Patel CB, Mountis MM, et al. INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profiling identifies ambulatory patients at high risk on medical therapy after hospitalizations for heart failure. Circ Heart Fail. 2016;9(11). **INTERMACS profiles, which were originally intended for patients receiving durable MCS, also can be used to identify high-risk patients managed with medical therapy.**
32. Ambardekar AV, Kittleson MM, Palardy M, et al. Outcomes with ambulatory advanced heart failure from the Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS) Registry. *The Journal of Heart and Lung Transplantation.* 2019 *In Press* https://doi.org/10.1016/j.healun.2018.09.021
33. Ambardekar AV, Forde-McLean RC, Kittleson MM, et al. High early event rates in patients with questionable eligibility for advanced heart failure therapies: results from the Medical Arm of Mechanically Assisted Circulatory Support (Medamacs) Registry. J Heart Lung Transplant. 2016;35(6):722–30.
34.•• Ambardekar AV, Thibodeau JT, DeVore AD, et al. Discordant perceptions of prognosis and treatment options between physicians and patients with advanced heart failure. JACC Heart Fail. 2017;5(9):663–71. **Among a majority of patients with stage D HF, neither patients nor physicians accurately predicted high-risk patients.**
35. Rogers JG, Boyle AJ, O'Connell JB, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: design and rationale of the ROADMAP clinical trial. Am Heart J 2015;169(2):205–210.e220.
36. Estep JD, Starling RC, Horstmanshof DA, Milano CA, Selzman CH, Shah KB, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: results from the ROADMAP study. J Am Coll Cardiol. 2015;66(16):1747–61.
37. Starling RC, Estep JD, Horstmanshof DA, Milano CA, Stehlik J, Shah KB, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: the ROADMAP study 2-year results. JACC Heart Fail. 2017;5(7):518–27.
38.• Lanfear DE, Levy WC, Stehlik J, et al. Accuracy of Seattle Heart Failure Model and HeartMate II risk score in non-inotrope-dependent advanced heart failure patients: insights from the ROADMAP study (risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients). Circ Heart Fail. 2017;10(5). **Commonly used prediction models did not adequately predict clinical worsening among non-inotrope-dependent stage D HF patients on optimal medical therapy**.
39. Shah KB, Starling RC, Rogers JG, Horstmanshof DA, Long JW, Kasirajan V, et al. Left ventricular assist devices versus medical management in ambulatory heart failure patients: an analysis of

INTERMACS profiles 4 and 5 to 7 from the ROADMAP study. J Heart Lung Transplant. 2018;37(6):706–14.
40. Pagani FD, Aaronson KD, Kormos R, Mann DL, Spino C, Jeffries N, et al. The NHLBI REVIVE-IT study: understanding its discontinuation in the context of current left ventricular assist device therapy. J Heart Lung Transplant. 2016;35(11):1277–83.
41. Aaronson KD, Stevenson LW, Pagani FD, Spino C, Kormos RL, Khalatbari S, et al. Identifying ambulatory advanced heart failure patients at high risk for death, LVAD or transplant at 1-year: how did the REVIVAL eligibility criteria perform? J Heart Lung Transplant. 2018;37(4):S195–6.
42. Gott M, Barnes S, Parker C, Payne S, Seamark D, Gariballa S, et al. Dying trajectories in heart failure. Palliat Med. 2007;21(2):95–9.
43. Palardy M, McLean R, Pamboukian S, Kittleson MM, Warner Stevenson L, Shah P, et al. The REVIVAL registry of ambulatory advanced heart failure: baseline characteristics. J Heart Lung Transplant. 2017;36(4):S211.
44. Alba AC, Agoritsas T, Jankowski M, Courvoisier D, Walter SD, Guyatt GH, et al. Risk prediction models for mortality in ambulatory patients with heart failure: a systematic review. Circ Heart Fail. 2013;6(5):881–9.
45. Cook JL, Colvin M, Francis GS, et al. Recommendations for the use of mechanical circulatory support: ambulatory and community patient care: a scientific statement from the American Heart Association. Circulation. 2017;135(25):e1145–58.
46. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol. 2014;63(8):747–62.
47. Baert A, De Smedt D, De Sutter J, et al. Factors associated with health-related quality of life in stable ambulatory congestive heart failure patients: systematic review. Eur J Prev Cardiol. 2018;25(5):472–81.
48. Pina IL, Di Palo KE, Ventura HO. Psychopharmacology and cardiovascular disease. J Am Coll Cardiol. 2018;71(20):2346–59.
49. Gathright EC, Goldstein CM, Josephson RA, Hughes JW. Depression increases the risk of mortality in patients with heart failure: a meta-analysis. J Psychosom Res. 2017;94:82–9.
50. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. 2011;123(18):2006–14.
51. Rogers JG, Patel CB, Mentz RJ, Granger BB, Steinhauser KE, Fiuzat M, et al. Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. J Am Coll Cardiol. 2017;70(3):331–41.
52. Allen LA, McIlvennan CK, Thompson JS, Dunlay SM, LaRue S, Lewis EF, et al. Effectiveness of an intervention supporting shared decision making for destination therapy left ventricular assist device: the DECIDE-LVAD randomized clinical trial effectiveness of an intervention supporting shared decision making for destination therapy left ventricular assist device effectiveness of an intervention supporting shared decision making for destination therapy left ventricular assist device. JAMA Intern Med. 2018;178(4):520–9.