Patients progressing to advanced heart failure (HF), despite optimal medical and pacing therapies, face poor survival and quality of life. After half a century of clinical development, mechanical circulatory support (MCS) devices have become an accepted treatment option. Initial approval for these devices was based on outcomes in patients with cardiogenic shock for whom death was imminent or in patients dependent on continuous intravenous inotropic therapy. Subjects were followed for at least 12 months or until death, mechanical support, or transplant. Baseline features, quality of life, and outcomes were compared according to INTERMACS profile. Mean age was 57 years, ejection fraction 18%, and 57% had HF >5 years, whereas 23% of subjects were INTERMACS profile 4, 32% profile 5, and 45% profile 6/7. At 1 year, only 47% of this ambulatory advanced HF cohort remained alive on medical therapy. Patients in INTERMACS profile 4 were more likely to die or require mechanical support, with only 52% of these patients alive without support after the first 6 months. Profile 6/7 patients had 1-year survival of 84%, similar to outcomes for contemporary destination left ventricular assist device recipients. Quality of life using the indexed EuroQol score was poor across profiles 4 to 7, although severe limitation was less common than for ambulatory patients enrolled in INTERMACS before ventricular assist device implantation.

Conclusions—Ambulatory patients with systolic HF, a heavy symptom burden, and at least 1 recent HF hospitalization are at high risk for death or left ventricular assist device rescue. INTERMACS profiles help identify ambulatory patients with advanced HF who may benefit from current mechanical support devices under existing indications. (Circ Heart Fail. 2016;9:e003032. DOI: 10.1161/CIRCHEARTFAILURE.116.003032.)

Key Words: heart failure ■ hospitalization ■ outcome measures ■ quality of life ■ registries
The largest potential public health benefits from MCS are anticipated in ambulatory patients where MCS can be used effectively with lower postoperative complication rates and improved cost-effectiveness. For this ambulatory population in whom death is not imminent, shared decision making about MCS also requires a more measured and individualized consideration of risks and benefits beyond survival. Current MCS decisions for ambulatory patients are seriously constrained by lack of information regarding expected outcomes for comparable patients on contemporary medical therapy without MCS. These uncertainties limit the comfort for physicians to refer and ambulatory patients to accept MCS. Recent attention to pump complication rates has also raised questions about the indications for implantation in ambulatory patients before inotrope dependence. There remains an urgent need to understand the outcomes of ambulatory advanced HF patients to provide context for MCS patient selection, informed consent, and policy decisions.

We sought to characterize the clinical features, quality of life, risk profiles, and competing outcomes in ambulatory patients with advanced HF who demonstrate high-risk features while on a strategy of oral medical therapy at MCS/transplant centers. INTERMACS profiles of patients requiring various levels of intravenous support have influenced selection and timing for MCS, but the utility of INTERMACS profiles for triage of patients on oral therapy has not yet been established. We evaluated the 1-year risk of death, MCS, or transplant stratified by baseline INTERMACS profile to better understand outcomes in the ambulatory advanced HF patients on optimal contemporary medical therapy.

Methods

Study Population

The Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS) Screening Pilot Study was a prospective observational study of patients with ambulatory advanced HF followed at 10 advanced HF programs in the United States. Each center had both a Joint Commission certified destination therapy left ventricular assist device (LVAD) program and a heart transplant program certified by the United Network of Organ Sharing. Subjects enrolled were aged 18 to 80 years, with New York Heart Association functional class III or IV limitation for 45 of the last 60 days, left ventricular ejection fraction ≤30%, and HF symptoms or diagnosis >12 months. All patients were on maximum tolerated doses of evidence-based HF medical therapies for >6 months or had a documented contraindication or intolerance to medication use.

Enrollment required subjects to have 2 unplanned HF hospitalizations in the last 12 months or 1 HF hospitalization plus at least 1 of the following high-risk features: exercise testing with peak oxygen uptake <55% predicted, or <16 mL/kg/min for men, <14 mL/kg/min for women; a 6-minute walk test distance of <300 m; B-type natriuretic peptide >800 pg/mL; serum sodium <135 mg/dL on 2 separate occasions at least 7 days apart; or an emergency department visit within 6 months for either ultrafiltration or intravenous diuretics. Among study subjects, 80% were enrolled based on 2 or more previous hospitalizations, 20% after at least 7 days apart; or an emergency department visit within 6 months.

In addition, patients had a prolonged QRS duration (>150 ms) with planned biventricular pacemaker placement or had received resynchronization within 90 days. The study was approved by the Institutional Review Board at each center. All subjects provided written informed consent before study participation, which included informed consent for telephone contact at 1 year if needed to assess vital status and outcomes.

Data Collection and Outcome Measures

After informed consent, 168 subjects were enrolled between September 2010 and April 2011. Comprehensive baseline data were recorded from usual care practices and included patient demographics and socioeconomic status, recent interventions and HF hospitalizations, along with hemodynamics and echocardiography when available within 6 months. Information was gathered from chart review and supplemented by patient history. INTERMACS patient profiles were assigned at enrollment by the treating clinician, according to methods previously described (Table 1). To compare with other risk scores in common use, Seattle Heart Failure Model (SHFM) score was calculated for each subject based on data collected within 3 months of study enrollment. Missing data were rare in the SHFM calculation, except for percentage lymphocytes (39/168), uric acid (99/168), and total cholesterol (45/168), which were not routinely collected in usual care practices. During SHFM calculation, these missing values were substituted by default values in the standard web-based SHFM. For comparison, mortality if LVAD implantation were to occur instead at the time of enrollment was estimated using the HeartMate II Risk Score (HMRS), which was the standard instrument for estimate post-LVAD risk at the time patients were enrolled. For HMRS calculation, an International Normalized Ratio (INR) of 1.0 was imputed for patients who were on warfarin, and all centers were high-volume ventricular assist device (VAD) implanting centers (>15/y).

At the enrollment visit, subjects completed the EuroQol-5D instrument for the assessment of health-related, disease-neutral quality of life. The widely validated tool contains a visual analog scale from 0 (worst imaginable health state) to 100 (best state), along with a 5-item descriptive system to assess problems with mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These 5 simple questions generate 243 distinct health states that determine an index score. The EuroQol index score ranges from 0 (death) to 1 (best imaginable health state). EuroQol data from this medically managed cohort were compared with preimplantation EuroQol assessments collected from patients receiving approved LVADs enrolled in the INTERMACS registry, including recipients in profile 4 (n=175) and profiles 5 to 7 (n=97) using data previously published.

All patients were followed for 1 year or until death, transplant or durable MCS. One subject withdrew informed consent during the study, and another was lost to follow-up, making a final study cohort of 166 patients for the analysis of 1-year event rates.

### Table 1. INTERMACS Profile Definitions for Ambulatory Patients on Oral Therapy

<table>
<thead>
<tr>
<th>Profile</th>
<th>Shorthand</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Resting symptoms</td>
<td>At home on oral therapy but with frequent symptoms of congestion at rest or with any activities of daily living</td>
</tr>
<tr>
<td>5</td>
<td>Exertion intolerant</td>
<td>Comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound, but without overt congestion</td>
</tr>
<tr>
<td>6</td>
<td>Exertion limited</td>
<td>Comfortable at rest without evidence of fluid overload and able to do some mild activities of daily living, but gets fatigued within a few minutes of any meaningful exertion</td>
</tr>
<tr>
<td>7</td>
<td>Advanced NYHA class III</td>
<td>Clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent</td>
</tr>
</tbody>
</table>

INTERMACS indicates Interagency Registry for Mechanically Assisted Circulatory Support.
Statistical Methods
Data analysis was performed with SAS (version 9.2, Cary, North Carolina). Continuous data were evaluated for normality, then Student t, 1-way ANOVA, or Mann–Whitney testing was performed for between-group comparisons as appropriate. Categorical data were compared with the Fisher exact test. Correlation between the EuroQol index score and the visual analog scale was performed using the Pearson coefficient. For the primary analysis, patients were stratified according to 3 INTERMACS patient categories: profile 4, profile 5, and profiles 6/7. The last 2 profiles were grouped because they are collectively thought to represent degrees of advanced New York Heart Association class III HF.

To calculate risks according to current scores, SHFM and HRMS were each separated into 3 groups. Risk with HF was stratified into moderate risk (estimated risk <17% at 1 year based on SHFM score <1.5), high risk (estimated mortality 17% to 40% at 1 year based on SHFM score 1.5–2.5), and very high risk (estimated mortality risk ≥40% based on SHFM score >2.5). For HRMS, thresholds for high, medium, and low risk were scores >2.48, 1.58 to 2.48, and <1.58, respectively, which correspond to estimated mortality at 90 days after MCS of 27%, 14%, and 6% and at 1 year of 42%, 28%, and 17%. For all participants, primary study end points of death, mechanical support, or heart transplantation were evaluated through 1 year. Competing outcomes methodology was used to estimate the cumulative incidence function of a patient moving into 1 of 3 mutually exclusive events. After stratification by baseline INTERMACS profile, the Kaplan–Meier method was used to estimate survival on oral medical therapies (censoring at mechanical support or transplant) along with freedom from death or MCS rescue (censoring at transplant only). Cox proportional hazard regression was used to evaluate the impact of INTERMACS profile on survival free of MCS rescue.

Results
Baseline Clinical Features
MedaMACS screening pilot subjects (n=166) had a mean age of 57 years, 47% had an ischemic cause, and 57% had HF diagnosis >5 years (Table 2). Confirming the advanced nature of HF in this population, the mean ejection fraction was 18%, the mean number of HF hospitalizations in the previous 6 months was 2.3, and among those with a right heart catheterization in the previous 6 months, the mean cardiac index was 2.1 L/min/m². Nearly half of participants (48%) had previously been evaluated for durable MCS or transplant, so the cohort may have encompassed those who may have been considered too sick or too well for advanced therapies.

Optimal contemporary medical therapy in this ambulatory advanced HF cohort included β-blockers (90%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (76%), and aldosterone antagonists (62%). Almost half (47%) had received cardiac resynchronization therapy, 78% had a defibrillator, and 35% had a previous cardiac surgery. The distribution of INTERMACS profiles included 22% in profile 4, 32% in profile 5, 34% in profile 6, and 12% in profile 7. Patients declared to be in a sicker INTERMACS profile at enrollment had more HF hospitalizations in the previous 6 months and were less likely to be receiving a β-blocker, although 81% were still tolerating β-blocker therapy.

Outcomes by Profile
Competing outcomes were modeled in Figure 1. By 1 year after enrollment, less than half (47%) of ambulatory advanced HF subjects were still alive on medical therapy. Death without MCS or transplant had occurred in 23%, 15% had undergone transplantation, and 15% had received durable MCS. At 1 year, 5 additional patients (3%) were on continuous inotropes.

Overall survival from an initial strategy of medical therapy was significantly lower with lower baseline INTERMACS profile (P=0.039) at both 6 months and 12 months (Figure 2). By 12 months of follow-up, only 60% of patients in INTERMACS profile 4 were alive on medical therapy without receiving MCS or transplant. In contrast, 84% of patients in profiles 6/7 were still alive on medical therapy at 12 months.

Survival free of MCS was also significantly lower with progressively sicker baseline INTERMACS profile (P<0.001; Figure 3). Among patients initially in INTERMACS profile 4, just over half (52%) were alive without VAD placement by 6 months and 39% were alive without VAD placement at 12 months of follow-up. Even after adjusting for β-blocker use, the number of HF hospitalizations in the previous 6 months, and SHFM score quartile, each successively lower INTERMACS profile was still associated with a markedly increased risk of death or MCS rescue through 1 year (hazard ratio, 1.72; 95% confidence interval, 1.20–2.49).

Elements of Decision Making for LVAD
Higher Event Rate on Medical Therapy Than Predicted by SHFM
The median (25th, 75th) SHFM score for the cohort at enrollment was 1.15 (0.54, 1.82), which corresponds to a median predicted HF mortality of 12% at 1 year, substantially lower than the 23% actually seen in this high-risk ambulatory population followed at MCS centers. The SHFM score did increase progressively with worsening INTERMACS profile (P=0.004). Only 7% carried the highest-estimated SHFM (SHFM >2.5). Combined event rates were considerable in each SHFM risk stratum. By 6 months after enrollment, risk of VAD, transplant, or death was 74% in the very high-risk SHFM group (score>2.5, with predicted mortality ≥40%), 42% in the high-risk group (SHFM score 1.5–2.5, with predicted mortality 17%–40%), and 23% in the remaining group (SHFM score <1.5, with predicted mortality <17%).

Predicted Mortality After LVAD
On the basis of the HMRS for estimated postoperative mortality after MCS, 8% were predicted to have a high post-MCS mortality risk, 22% intermediate risk, and 70% low risk. In contrast to the event rates with an initial strategy of medical therapy outlined above, there was no significant difference in estimated risk of VAD according to INTERMACS profile group (P=0.31; Figure 4).

Quality of Life Differences Between Medical and VAD Populations
At the baseline visit, 162 patients (96%) completed the full EuroQol-5D instrument. Most ambulatory advanced HF patients had some or extreme limitation in mobility (75%) and usual activities (80%), whereas 30% expressed some limitation in self-care. Pain/discomfort (60%) and anxiety/depression (61%) were also common. Subjects with worse INTERMACS profile as assigned by physicians were significantly more likely to have a reduced EuroQol index score based on the patient answers to the 5 domains (P<0.001; Figure 5). Patient...
assessment of their overall quality of life using the EuroQol visual analog scale score had a mean of 52, which was not different across profiles. Overall, there was modest positive correlation between EuroQol index score and visual analog scale in this cohort ($r=0.41$; 95% confidence interval, 0.27–0.53).

Generic health-related quality of life as assessed by the EuroQol-5D instrument could be compared between high-risk ambulatory patients in INTERMACS profiles 4 to 7 and ambulatory patients in the INTERMACS registry who completed a quality of life assessment before receiving LVAD.

Table 2. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Total Cohort (n=166)</th>
<th>INTERMACS Profile</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 (n=37)</td>
<td>5 (n=53)</td>
<td>6/7 (n=76)</td>
</tr>
<tr>
<td>Age, y</td>
<td>57 (13)</td>
<td>56 (12)</td>
<td>57 (13)</td>
</tr>
<tr>
<td>Male</td>
<td>71</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>White race</td>
<td>72</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>Married</td>
<td>64</td>
<td>57</td>
<td>68</td>
</tr>
<tr>
<td>College education</td>
<td>36</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Currently used</td>
<td>15</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>HF diagnosis &gt;5 y</td>
<td>57</td>
<td>64</td>
<td>46</td>
</tr>
<tr>
<td>Ischemic cause</td>
<td>46</td>
<td>51</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>45</td>
<td>32</td>
<td>51</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>36</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.6 (0.7)</td>
<td>1.6 (0.7)</td>
<td>1.6 (0.6)</td>
</tr>
<tr>
<td>Serum sodium, mg/dL</td>
<td>136 (4)</td>
<td>135 (5)</td>
<td>136 (4)</td>
</tr>
<tr>
<td>Estimated GFR, mL/min</td>
<td>57 (25)</td>
<td>57 (25)</td>
<td>57 (25)</td>
</tr>
</tbody>
</table>

Heart failure severity

<table>
<thead>
<tr>
<th>Ejection fraction, %</th>
<th>18 (6)</th>
<th>17 (5)</th>
<th>17 (7)</th>
<th>18 (6)</th>
<th>0.51</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP, pg/mL</td>
<td>779 (370, 1450)</td>
<td>714 (396, 1237)</td>
<td>965 (519, 2180)</td>
<td>684 (280, 1130)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.1 (0.6)</td>
<td>2.0 (0.5)</td>
<td>2.1 (0.5)</td>
<td>2.2 (0.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>Peak $V_s$ mL/kg/min</td>
<td>12.6 (4.0)</td>
<td>13.1 (4.8)</td>
<td>11.7 (3.1)</td>
<td>13.6 (4.3)</td>
<td>0.61</td>
</tr>
<tr>
<td>HF hospitalization in last 6 mo</td>
<td>2.3 (1.0)</td>
<td>2.5 (1.1)</td>
<td>2.5 (1.0)</td>
<td>2.1 (1.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous VAD/transplant evaluation</td>
<td>48</td>
<td>57</td>
<td>51</td>
<td>41</td>
<td>0.11</td>
</tr>
<tr>
<td>NYHA class</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>45</td>
<td>22</td>
<td>33</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>40</td>
<td>35</td>
<td>58</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
<td>43</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Seattle HF model score</td>
<td>1.20 (0.88)</td>
<td>1.56 (0.85)</td>
<td>1.23 (0.75)</td>
<td>0.99 (0.79)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Medical and device therapies

| β-adrenergic antagonist | 90 | 81 | 85 | 95 | 0.03 |
| ACE inhibitor or ARB    | 77 | 70 | 74 | 83 | 0.11 |
| Hydralazine plus nitrate | 17 | 14 | 25 | 14 | 0.29 |
| Aldosterone antagonist  | 62 | 68 | 62 | 58 | 0.61 |
| Loop diuretic           | 95 | 100| 94 | 93 | 0.33 |
| Cardiac resynchronization therapy | 46 | 54 | 49 | 41 | 0.37 |
| Implantable defibrillator | 78 | 76 | 70 | 86 | 0.09 |
| Previous ICD shock      | 42 | 35 | 37 | 29 | 0.49 |

Data reported as mean (SD) or percentage. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry of Mechanically Assisted Circulatory Support; NYHA, New York Heart Association; and VAD, ventricular assist device; $V_s$, oxygen consumption.
medical patients in profile 4 (n=37) had similar degree of limitation in mobility, usual activity, anxiety/depression, and pain/discomfort compared with LVAD registry recipients who were implanted as profile 4, although LVAD registry recipients described greater problems with self-care, and an average VAS of only 33 compared with 50 in medical patients. By contrast, the small number of INTERMACS registry patients in profiles 5 to 7 who received LVAD expressed significantly greater burden in mobility, self-care, usual activities, and anxiety/depression before LVAD compared with MedaMACS patients in profiles 5 to 7. Preimplant LVAD registry patients in all INTERMACS profiles 4 to 7 expressed a significantly poorer quality of life according to EuroQol visual analog scale when compared with high-risk ambulatory patients on medical management in MedaMACS (Figure 6).

**Discussion**

More than half of the patients with ambulatory advanced chronic systolic HF and a recent HF hospitalization had died, undergone transplantation, or received durable MCS over the ensuing year. Although initially intended for use in patients receiving MCS, INTERMACS patient profiles encompass multiple domains of risk and provided relevant risk stratification in this medically managed cohort of advanced HF patients at home on oral medical therapy. Lower INTERMACS patient profiles were also associated with a higher risk of death without MCS or transplant. In particular, eligible profile 4 patients should be offered LVAD therapy because continued medical therapy is associated with high event rates and low quality of life.

The present study represents the largest published cohort of high-risk ambulatory advanced HF patients in INTERMACS profiles 4 to 7 receiving a strategy of oral medical management at VAD/transplant centers. Patients enrolled in this study, each of whom had at least 1 HF hospitalization within the previous year, were not currently receiving MCS for various reasons, including relative contraindications, their own preferences, or their characterization as less sick either by perception or by objective criteria. The integrated assessment at experienced MCS centers as reflected by INTERMACS profile confirmed a gradient of risk consistent with that provided by a complex risk score with multiple components (the SHFM). The estimated magnitude of risk in the advanced HF population that might be considered for MCS was underestimated using the Seattle Model in this study and in previously reported populations, suggesting that SHFM should

![Figure 1](http://circ.ahajournals.org/doi/10.1161/CIRCHEARTFAILURE.116.005096)  
**Figure 1.** Competing events. Mutually exclusive end points of death, ventricular assist device (VAD), or transplant (Tx) were tracked through 1 year, with the cumulative percentage of events at any given time point equal to 100%.

![Figure 2](http://circ.ahajournals.org/doi/10.1161/CIRCHEARTFAILURE.116.005096)  
**Figure 2.** Survival according to INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile. Estimated survival was modeled through 1 year using the Kaplan–Meier method with censoring at either ventricular assist device (VAD) or transplant. Survival was significantly different between patient profile groups (P=0.039).
not be used in isolation to decide on elective MCS. In this medically managed cohort, INTERMACS profiles also tracked with most domains of the validated health-related quality of life metrics (EuroQol index score), although the ambulatory groups reported similar levels of pain/discomfort and the integrated quality of life as assessed by the visual analog score. The significant differences in key parameters between the profiles, including greater intolerance to neurohormonal antagonists and greater frequency of HF hospitalization in the lower INTERMACS profiles, help to validate the profiles; yet, the considerable overlap in features within each profile emphasizes that profile alone should not be used to adjudicate risk in this complex population.

The present study helps to refine selection for MCS from within the ambulatory systolic HF population with advanced disease as reflected by frequent HF hospitalization. INTERMACS profile 4 patients had a strikingly high event rate, with 48% dying or receiving rescue MCS by just 6 months of follow-up compared with only 22% of profile 5 patients. The traditional reimbursement indication for destination therapy LVAD set by the Center for Medical and Medicaid service has included INTERMACS profile 4 or 5 patients provided limitation is documented by reduced peak oxygen consumption. Recent publications highlighting adverse event rates with MCS and the FDA warning about complications across multiple vendor platforms have reopened debate about the appropriateness of MCS use before inotrope dependence. However, our data strongly suggest that appropriately selected high-risk patients in profile 4 and some in profile 5 should continue to be considered for current LVADs on the basis of a high anticipated mortality risk and poor quality of life in the absence of surgical HF therapies.

The 47% one-year survival without VAD or transplant at 1 year in this 166 patient study is lower than the 1-year survival of 63% noted in the 103 patients opting for medical management rather than LVAD in the ROADMAP study (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients). The current study includes a greater proportion of INTERMACS profile 4 patients, for whom medical

Figure 3. Survival free of ventricular assist device (VAD) rescue according to INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile. Estimated survival or VAD was modeled through 1 year using the Kaplan–Meier method with censoring at transplant. Survival free of VAD rescue was significantly different according to INTERMACS profile (P<0.001).
therapy is more likely to fail early after enrollment. The average visual analog scale value for quality of life at baseline was 50 in this study, lower than the 60 reported in ROADMAP for the medically managed group. It should be noted that some of the higher mortality may relate to underlying frailty or other comorbidity because eligibility for LVAD was not an explicit inclusion criterion for this study, although patients were excluded if they carried a noncardiac diagnosis anticipated to limit 2-year survival or had a primary functional limitation that was not cardiovascular.

This is the largest study to date characterizing the degree of limitation of health-related quality of life in high-risk ambulatory patients on medical therapy for HF. In aggregate, these high-risk ambulatory patients report limitation in multiple domains of quality of life, with INTERMACS profile 4 patients on medical management describing burdens similar to those receiving LVAD therapy. As might be expected, those patients’ triages to LVAD therapy in profiles 5 to 7 had a significantly great burden of limitation than those on medical therapy, as well as reduced overall quality of life, which may explain why LVAD implantation was pursued for these patients. Patients in lower INTERMACS have previously been reported to be more willing to consider LVAD and consistent value anticipate improvements in quality of life from an LVAD at least as much as survival. In high-risk ambulatory patients under review for LVAD candidacy who report a particularly poor patient-reported quality of life, there may be a justifiable role for earlier consideration of LVAD implantation before the development of inotrope dependence in eligible patients.

Survival at 1 year in INTERMACS after destination therapy with current LVADs is similar to the 84% survival rate seen for profile 6 to 7 patients receiving an initial strategy of medical therapy in this study. Widespread expansion of LVAD indications into the less sick INTERMACS profiles 6/7 will likely await

Figure 5. EuroQol-5D index score by INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile. EuroQol index score from best (1) to worst (0) possible health utility were quantified for all patients and stratified by INTERMACS profile. There was a significant trend to lower health utility with lower INTERMACS patient profile (P<0.001).

Figure 6. Quality of life in ambulatory advanced heart failure. Limitation across the 5 domains of the EuroQol health-related quality of life instrument (A–E) and visual analog scale (VAS; F) was compared between participants in the Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS) screening pilot (MM, blue) and the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry (IM, turquoise). Degree of limitation in each EuroQol domain was categorized as extreme (dark), some (light), or none (not shown). Responses were stratified according to INTERMACS profile group. Analysis included high-risk ambulatory patients on medical management within profile 4 (n=37) and profiles 5 to 7 (n=125) along with left ventricular assist device (LVAD) recipients in profile 4 (n=175) and profiles 5 to 7 (n=97), as previously reported by Grady et al. Adapted from Grady et al with permission of the publisher. Copyright © 2014 Elsevier.
innovative next-generation support device with lower complication rates. Although operative survival has improved with focus on better INTERMACS profiles, the long-term complication rates of bleeding, stroke, and VAD thrombosis have been similar regardless of baseline profile. Integration of quality of life indices will likely be required to distinguish outcomes between contemporary medical management and currently approved devices in profiles 6/7. The closing of the NHLBI-sponsored REVIVE-IT (Randomized Evaluation of VAD Intervention before Inotropic Therapy) study deprived the HF community of important information on a medically managed cohort of patients in parallel to device therapy.20 The present study, along with the recently published industry-sponsored ROADMAP trial, addresses the important knowledge gap about how best to triage high-risk ambulatory patients in whom MCS can be used electively for long-term benefit with lower anticipated complication rates and improved cost-effectiveness.18 For this less sick population in whom death is not imminent, shared decision making about MCS will require more measured and individualized consideration of risks and benefits beyond survival.

This study has several important limitations that must be considered when interpreting these results. First, these high-risk ambulatory advanced HF patients were enrolled at quaternary care VAD/transplant centers, so results may not be applicable outside this setting. INTERMACS profiling may also have exerted a floor and ceiling effect to sort patients of varying disease severity and should be interpreted contingent on the entry criteria of this study, including frequent previous HF hospitalizations, and within the context of overlapping clinical features between profiles. The sample size is also modest for an attempt to distinguish outcomes in 3 groups of patients. Because patients were not listed for transplant at enrollment and many had not been evaluated for MCS, this cohort is composed of patients considered to be either too sick or too well for advanced cardiac therapies. Longitudinal changes in patient characteristics, changes in profile, details of hospitalizations, and other adverse events, as well as triggers for MCS or transplant listing, could not be evaluated. Patient profiles at the time of transplant or LVAD were not available. A baseline assessment may not provide enough resolution to adjudicate risk in ambulatory patients with dynamic clinical trajectories. For the several SHFM variables with frequent missing data, multiple imputation was not used in favor of the widely used default values derived from a larger ambulatory HF cohort. Lastly, outcomes relevant to ambulatory patients with advanced HF extend beyond the 1-year horizon of follow-up in this study and will likely require careful integration of quality of life metrics.

These preliminary screening pilot data have served as the foundation for the design of a prospective, longitudinal, multi-centered study to map the trajectories of ambulatory advanced HF. The MedaMACS study will have comprehensive serial follow-up through 2 years and will generate detailed patient-level information on functioning, frailty, and quality of life, with outcome measures in parallel to those established in the INTERMACS registry.21 In many ambulatory patients, particularly profiles 5 to 7, in whom death may not be imminent, considerations of quality of life and functioning may be as important as survival in deciding when to proceed with MCS.22 Novel composite end points integrating both survival and quality of life will likely be needed to distinguish medical and device therapy in so-called lower risk advanced HF populations. MedaMACS study will facilitate better alignment between approved MCS devices and contemporary medical therapy and inform the complex matrix of decisions facing patients and their providers.

In the meantime, ambulatory patients with advanced HF should receive systematic education about the expectations with chronic HF, such as at an annual HF review as advocated by a recent AHA scientific statement on decision making in advanced HF.23 Although still clinically compensated, potentially appropriate patients should undergo orientation about MCS.24 From the first consideration of device therapy, emphasis should be placed on the anticipated differences between ongoing medical therapy and MCS with respect to both survival and quality of life to elucidate patient preferences. Ongoing research will better inform how best to educate patients and their families about the anticipated risk and trade-offs of device versus medical therapy such as the DECIDE-LVAD trial (Decision Support Intervention for Patients and Caregivers Offered Destination Therapy Heart Assist Device) (https://clinicaltrials.gov/ct2/show/NCT02344576).

In conclusion, ambulatory patients with chronic systolic HF, a heavy symptom burden, and at least 1 recent HF hospitalization are at high risk of death or progression to advanced cardiac therapies, despite optimal contemporary medical therapy. INTERMACS profiles are a useful shorthand for describing disease severity in patients with ambulatory advanced HF. Survival in patients who are INTERMACS profile 4 is lower than with contemporary LVADs, confirming the appropriateness of MCS use under existing indications and suggesting an opportunity for expanded deployment in appropriately selected patients.

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References

Profiles in Ambulatory Advanced Heart Failure


CLINICAL PERSPECTIVE

Patients with systolic heart failure (HF) are increasingly being considered as candidates for mechanical circulatory support (MCS) even before the dependence on inotropes to support hemodynamics. Current decisions surrounding MCS deployment in ambulatory patients are seriously constrained by lack of information about expected outcomes for comparable patients on contemporary oral medical therapy without MCS. In this prospective observational study of usual care in patients with advanced systolic HF followed at MCS/transplant centers, ambulatory patients with a heavy symptom burden and at least 1 recent HF hospitalization were at high risk of death or the need for MCS, despite optimal medical therapy. By 1 year of follow-up in this study, more than half of the patients with ambulatory advanced systolic HF had died, undergone transplantation, or received durable MCS. The INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) patient profiles are a shorthand for describing symptom burden and disease trajectory in patients with advanced HF. Although initially intended for use in patients receiving MCS, INTERMACS patient profiles encompass multiple domains of risk and, when assigned by experienced HF clinicians, provided relevant risk stratification in this medically managed cohort with a recent HF hospitalization. Survival in patients who were INTERMACS profile 4 was lower than those with contemporary left ventricular assist devices, confirming the appropriateness of MCS use under existing indications and suggesting an opportunity for expanded deployment in appropriately selected patients.
INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) Profiling Identifies Ambulatory Patients at High Risk on Medical Therapy After Hospitalizations for Heart Failure

Garrick C. Stewart, Michelle M. Kittleson, Parag C. Patel, Jennifer A. Cowger, Chetan B. Patel, Maria M. Mountis, Frances L. Johnson, Maya E. Guglin, J. Eduardo Rame, Jeffrey J. Teuteberg and Lynne W. Stevenson

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