

FEATURED PAPER

Outcomes with ambulatory advanced heart failure from the Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS) Registry



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BACKGROUND: The outlook for ambulatory patients with advanced heart failure (HF) and the appropriate timing for left ventricular assist device (LVAD) or transplant remain uncertain. The aim of this study was to better understand disease trajectory and rates of progression to subsequent LVAD therapy and transplant in ambulatory advanced HF.

METHODS: Patients with advanced HF who were New York Heart Association (NYHA) Class III or IV and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Profiles 4 to 7, despite optimal medical therapy (without inotropic therapy), were enrolled across 11 centers and followed for the end-points of survival, transplantation, LVAD placement, and health-related quality of life. A secondary intention-to-treat survival analysis compared outcomes for MedaMACS patients with a matched group of Profile 4 to 7 patients with LVADs from the INTERMACS registry.

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RESULTS: Between May 2013 and October 2015, 161 patients were enrolled with INTERMACS Profiles 4 (12%), 5 (32%), 6 (49%), and 7 (7%). By 2 years after enrollment, 75 (47%) patients had reached a primary end-point with 39 (24%) deaths, 17 (11%) undergoing LVAD implantation, and 19 (12%) receiving a transplant. Compared with 1,753 patients with Profiles 4 to 7 receiving LVAD therapy, there was no overall difference in intention-to-treat survival between medical and LVAD therapy, but survival with LVAD therapy was superior to medical therapy among Profile 4 and 5 patients ($p = 0.0092$). Baseline health-related quality of life was lower among patients receiving a LVAD than those enrolled on continuing oral medical therapy, but increased after 1 year for survivors in both cohorts.

CONCLUSIONS: Ambulatory patients with advanced HF are at high risk for poor outcomes, with only 53% alive on medical therapy after 2 years of follow-up. Survival was similar for medical and LVAD therapy in the overall cohort, which included the lower severity Profiles 6 and 7, but survival was better with LVAD therapy among patients in Profiles 4 and 5. Given the poor outcomes in this group of advanced HF patients, timely consideration of transplant and LVAD is of critical importance.

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Despite widespread use of evidence-based therapies, morbidity and mortality from systolic heart failure (HF) remain high. Over the last decade, breakthroughs in mechanical circulatory support technology have extended survival and improved quality of life in selected patients with advanced HF, as chronicled in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report.¹ Most patients receiving left ventricular assist devices have cardiogenic shock (INTERMACS Patient Profiles 1 or 2) or dependence on intravenous inotropic therapy (Profile 3), in whom LVAD therapy has clearly been shown to extend survival currently classified as compared with ongoing medical treatment.^{2,3} However, decisions surrounding appropriate use and timing of LVAD therapy in “less-sick” ambulatory patients with advanced HF on oral therapy without inotropic support (Profiles 4 to 7) are challenging, in part because of the information gap surrounding the trajectory of the disease.

It is also important to appreciate this disease trajectory in advanced HF to better inform discussions with patients. Given the complexities inherent in treating advanced HF patients with LVAD or cardiac transplantation, patient-centered care requires that we understand the myriad of possible outcomes, including adverse events.^{4–6} Balancing the risk and benefits of continued medical management against those associated with surgical interventions such as LVAD or transplant remains the central decision in advanced HF management.

Thus, the 2 primary aims of the Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS) study were to identify and study a cohort of ambulatory patients with advanced HF on oral medical and electrical therapies to better characterize prognosis and disease trajectory during follow-up at experienced centers offering LVAD therapy, and to facilitate real-world contemporary comparison of optimal medical vs LVAD therapy, utilizing the INTERMACS registry.¹ We hypothesized that the event rate would be high in patients with advanced HF, even if they were ambulatory and without the need for long-term inotropic infusion. We further hypothesized that it may be possible to identify a subgroup of these patients likely to have better outcomes with LVAD therapy.

Methods

Patient selection

Ambulatory patients with advanced HF (New York Heart Association Class III and IV, INTERMACS Patient Profiles 4 through 7) were enrolled in the prospective, observational MedaMACS study from May 2013 to October 2015 across 11 centers in the United States offering advanced HF management, including LVAD and cardiac transplantation programs. Study entry criteria have been published and are provided in Figure S1 (refer to the Supplementary Material available online at www.jhltonline.org/) and included patients with chronic advanced HF (diagnosis for at least 1 year and on evidence-based medications for at least 3 months unless documented contraindication or intolerance) and 1 previous HF hospitalization in the preceding year. Inclusion required at least 1 additional high-risk feature, including: (1) an additional HF-related hospitalization in the previous year for a total of at least 2 hospitalizations; (2) high brain natriuretic peptide (BNP) level (BNP > 1,000 pg/ml or N-terminal pro-BNP [NT-proBNP] > 4,000 pg/ml); (3) poor functional status as assessed by cardiopulmonary exercise testing or 6-minute walk; or (4) a high predicted mortality according to the Seattle HF model.^{7,8} Key exclusion criteria were current intravenous inotrope therapy, active listing for heart transplant, a congenital heart defect, a diagnosis of cardiac amyloidosis, or a non-cardiac diagnosis anticipated to limit survival or functional status. All participating institutions were required to comply with local regularity and privacy guidelines and to submit the MedaMACS protocol for review and approval by their institutional review boards. This MedaMACS study from 2013 to 2015 is distinct from the screening pilot feasibility study that enrolled patients in a smaller group of centers between October 2010 and April 2011.^{9–11}

Methods

Study design and outcome assessment

Baseline demographics, clinical characteristics, laboratory, echocardiography, hemodynamic, and functional status data were collected at enrollment. The primary end-points of the MedaMACS study were mortality on medical therapy or progression to LVAD placement or cardiac transplantation. Secondary end-points included hospitalization, inotrope utilization, and measures of generic health-related quality of life, as assessed with the Euro-QoL Visual Analog Scale (VAS). These measures and interval

events were assessed at 1 month, 1 year, and 2 years after entry into the study. Additional phone calls to capture interval events were made at 6 and 18 months after enrollment. Originally, data were to be collected prospectively for patients up to a study end-point or the pre-specified 2-year follow-up period; however, due to discontinuation of funding for ongoing data collection, the study ended on December 2016 and this report represents analysis of all available data collected to this date.

Registry-based comparison of medical vs LVAD therapy

To compare real-world, contemporary outcomes of medical therapy vs LVAD therapy, patients in MedaMACS were compared with patients enrolled in the INTERMACS registry who were listed as Profile 4 to 7 at the time of LVAD implantation.¹ Specifically, the INTERMACS registry was queried during a similar time period from January 2012 to December 2016. We chose to focus on only those patients in INTERMACS who received a primary durable LVAD implant and excluded patients receiving a total artificial heart or biventricular assist device. An intention-to-treat actuarial survival analysis was performed comparing the MedaMACS and INTERMACS outcomes for the entire group of Profile 4 to 7 patients and then after pre-specified stratification by INTERMACS patient profile. In addition, baseline and changes in health-related quality of life were determined for survivors in both MedaMACS and INTERMACS registries. To address potential biases with any missing quality-of-life data, comparisons between medical vs LVAD therapy were also made using a combined end-point of survival with good quality of life among those patients who completed the quality-of-life assessments.

Statistical analysis

All statistical analyses were performed centrally at the University of Alabama at Birmingham Data and Clinical Coordinating Center. Numerical data are reported as mean \pm standard deviation or as number (percent). Univariate comparisons between the cohorts of patients based on INTERMACS profile at enrollment were performed using the chi-square test or Fisher's exact test for categorical variables and the one-way analysis of variance test for continuous variables. For the entire MedaMACS study population, Kaplan–Meier survival curves were used to demonstrate: (1) overall unadjusted actuarial survival (with patients censored at the time of transplant, LVAD placement, or last follow-up); (2) survival without LVAD (with patients censored at the time of transplant or last follow-up); and (3) survival without LVAD or transplant (with patients censored at the time of last follow-up). Within the MedaMACS study population, Kaplan–Meier survival curves and log-rank tests were used to demonstrate unadjusted survival differences based on INTERMACS profile at enrollment, with comparisons made between individual profiles as well as Profile 4 to 5 vs Profile 6 to 7.

In addition, Kaplan–Meier survival curves and log-rank tests were used to compare intention-to-treat actuarial survival among medical therapy patients in MedaMACS and LVAD therapy patients in INTERMACS. For medical therapy, patients were censored at the time of transplant, LVAD placement, or last follow-up. For LVAD therapy, patients were censored at the time of LVAD explant for recovery, transplant, or last follow-up. Pre-specified comparisons between medical and LVAD therapy were also made based on patient profile at the time of enrollment.

Comparisons were made among the individual patient profiles (Profiles 4, 5, 6, and 7) as well as by combining patient Profiles 4 and 5 and Profiles 6 and 7, due to the small number of patients in each of these individual groups. SAS version 9.4 software (SAS, Inc., Cary, NC) was used for all statistical analysis.

Results

Baseline characteristics of the MedaMACS cohort

A total of 161 patients were enrolled between May 2013 and October 2015. The cohort had a mean age of 59 years, left ventricular ejection fraction (LVEF) of 21%, and NT-proBNP of 5,365 pg/ml, with 32% of patients non-Caucasian and 34% female (Table 1). Reflective of an advanced HF population, INTERMACS patient profiles at enrollment were as follows: Profile 4, 12%; Profile 5, 32%; Profile 6, 49%; and Profile 7, 7%. INTERMACS profiles assigned by treating physicians at enrollment tracked with functional status and quality of life, with Profile 4 patients having worse measures of functional status and lower quality-of-life scores than other ambulatory patients on oral therapy (Table 2).

Primary and secondary end-points of the entire MedaMACS study population

One-year primary and secondary end-point data were available for 143 (89%) of the original 161 patients. Of the 18 (11%) patients without 1-year outcomes data, 8 withdrew consent for the study and 10 transferred their care to a center not participating in the MedaMACS study. Of the 161 total participants, 55 (34%) had a primary end-point after 1 year. This included 27 (17%) deaths, 13 (8%) LVAD implants, and 15 (9%) transplants (Table 3). This cohort of advanced HF patients also had substantial morbidity, with an average of 1.7 additional hospitalizations per patient. Fifty-seven percent of patients required at least 1 rehospitalization for HF and many required use of continuous intravenous inotropes (Table 3).

Additional follow-up data were collected for patients until a study end-point, a pre-specified 2-year follow-up period, or the end of the study period in December 2016. As enrollment continued until October of 2015, 2-year follow-up data were not available for every enrolled patient. Of the initial 161 patients, 75 reached a study end-point (39 deaths, 17 LVAD implantations, and 18 transplants), 18 were lost to follow-up (as noted earlier, 8 withdrew consent and 10 transferred care), and 42 did not reach the full 2-year mark due to the end of study funding on December 2016. Survival curves based on the maximal duration of follow-up for each patient revealed that this ambulatory advanced HF patient population continued a downward trajectory with longer follow-up, with 24% mortality after 2 years (Figure 1A). In addition, 35% of patients had either died or undergone LVAD implantation by 2 years (Figure 1B). Similarly, the rate of death, LVAD placement, and transplantation remained high, as only 53% of patients were alive without a LVAD or transplant 2 years after enrollment (Figure 1C).

Table 1 Baseline Patient Characteristics at Enrollment Into the MedaMACS Study Compared With Pre-implant Characteristics of Patients in Profiles 4 Through 7 With LVAD Implant and Enrolled in the INTERMACS

	MedaMACS study (N = 161)	INTERMACS (N = 1,753)
Demographics		
Age (years)	59 ± 11	61 ± 12
Female gender	34%	18% ^a
Non-Caucasian race	32%	NA
Married or domestic partnership	60%	71% ^a
Heart failure characteristics		
Ischemic etiology of cardiomyopathy	39%	52% ^a
Idiopathic dilated cardiomyopathy	39%	28% ^a
Other etiology of cardiomyopathy	22%	20%
Implantable cardioverter-defibrillator	85%	89%
Cardiac resynchronization therapy	31%	NA
Inotrope therapy required in preceding 6 months	18%	NA
Number of cardiac hospitalizations in preceding year		
1	29%	32%
2	38%	34%
3	16%	15%
4 or more	17%	N/A
Unknown	0%	19%
INTERMACS patient profile		
Profile 4	12%	80% ^a
Profile 5	32%	13% ^a
Profile 6	49%	4% ^a
Profile 7	7%	3% ^a
Medication usage at enrollment		
ACE inhibitor/angiotensin-receptor blocker	60%	38% ^a
β-blockers	90%	77% ^a
Aldosterone antagonist	64%	50% ^a
Loop diuretics	93%	88%
Digoxin	49%	N/A
Laboratory values		
NT-proBNP (pg/ml)	5,365 ± 5,065	829 ± 893 ^a
Sodium (mmol/liter)	137 ± 4	137 ± 4
Blood urea nitrogen (mg/dl)	35 ± 20	27 ± 15 ^a
Creatinine (mg/dl)	1.5 ± 0.6	1.4 ± 0.7 ^a
Alanine aminotransferase (U/liter)	34 ± 43	40 ± 80
Aspartate aminotransferase (U/liter)	33 ± 24	34 ± 53
Total bilirubin (mg/dl)	1.2 ± 0.8	1.0 ± 0.8
Total cholesterol (mg/dl)	131 ± 43	153 ± 266
Uric acid (mg/dl)	9.6 ± 5.9	7.9 ± 2.6
Hemoglobin (g/dl)	12.7 ± 2.4	12.2 ± 2.0 ^a
Echocardiographic and hemodynamic data		
Left ventricular ejection fraction (%)	21 ± 7	10 ± 7 ^a
Left ventricular dimension diastole (cm)	6.5 ± 0.9	6.8 ± 1.0 ^a
Heart rate (beats/min)	79 ± 14	79 ± 15
Systolic blood pressure (mm Hg)	111 ± 15	109 ± 16
Diastolic blood pressure (mm Hg)	68 ± 11	66 ± 12 ^a
Right atrial pressure (mm Hg)	11 ± 6	12 ± 8
Pulmonary artery systolic pressure (mm Hg)	52 ± 13	48 ± 15 ^a
Pulmonary artery diastolic pressure (mm Hg)	25 ± 8	22 ± 9*
Pulmonary wedge pressure (mm Hg)	21 ± 8	22 ± 9
Cardiac output (liters/min)	4.5 ± 1.4	4.3 ± 1.4
Cardiac index (liters/min/m ²)	2.2 ± 0.7	2.3 ± 1.0

(continued)

Table 1 (Continued)

	MedaMACS study (N = 161)	INTERMACS (N = 1,753)
Baseline functional and quality-of-life status		
6-minute walk (m)	196 ± 156	304 ± 1,125
Gait speed (m/s)	1.0 ± 0.4	1.1 ± 0.5
Peak oxygen consumption (ml/kg/min)	12.1 ± 4.6	19.0 ± 8.2
EuroQol 5D Index score	0.69 ± 0.19	0.68 ± 0.21
EuroQol Visual Analog Scale	56 ± 21	43 ± 24 ^a
KCCQ score	51 ± 10	36 ± 20 ^a

ACE, angiotensin-converting enzyme; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; KCCQ, Kansas City Cardiomyopathy Questionnaire; MedaMACS, Medical Arm of the Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; NA, data not available (these variables were not collected in INTERMACS).

^a*p* < 0.01 for comparison of MedaMACS vs INTERMACS.

Table 2 INTERMACS Patient Profiles at Enrollment Into the MedaMACS Study Track With Functional Status and Quality of Life

	Profile 4 (N = 21)	Profile 5 (N = 49)	Profile 6 (N = 76)	Profile 7 (N = 15)
Age (years)	58 ± 10	60 ± 11	59 ± 11	57 ± 9
Ejection fraction (%)	21 ± 8	21 ± 7	21 ± 7	22 ± 6
NT-proBNP (pg/ml)	6,496 ± 4,617	6,407 ± 6,952	4,997 ± 3,908	3,564 ± 5,946
6-minute walk (m) ^a	166 ± 143	143 ± 140	239 ± 154	212 ± 192
Gait speed (m/s) ^a	0.8 ± 0.3	0.9 ± 0.5	1.1 ± 0.4	1.4 ± 0.3
Peak VO ₂ (ml/kg/min) ^a	9.8 ± 4.1	10.9 ± 3.1	13.2 ± 5.5	12.9 ± 1.0
EuroQol 5D Index ^a	0.52 ± 0.21	0.70 ± 0.15	0.72 ± 0.19	0.73 ± 0.19
EuroQol VAS ^a	45 ± 20	54 ± 21	59 ± 21	60 ± 17
KCCQ score	52 ± 10	52 ± 12	50 ± 8	48 ± 14

KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide; VAS, Visual Analog Scale; VO₂, oxygen consumption.

^a*p* < 0.05 for comparison across INTERMACS patient profiles.

Despite the differences in baseline measures of functional status among the different INTERMACS patient profiles, there were not clear statistical differences in 2-year survival stratified by patient profile at the time of enrollment, which may have been related to small patient numbers among individual profiles (see [Figure S2](#) in Supplementary Material online). When comparisons were made between Profile 4 or 5 vs Profile 6 or 7, there was a

trend for poorer outcomes among lower patient profiles, which did not reach statistical significance ([Figure 2](#)).

Survival with medical vs LVAD therapy

A total of 10,139 patients received a primary durable LVAD between January 2012 and December 2016 (excluding total artificial hearts and biventricular assist devices). The majority (8,386 patients) were INTERMACS Profile 1 to 3 at the time of LVAD implant and 1,753 patients were Profile 4 to 7 (see [Figure S3](#) in Supplementary Material online). These 1,753 LVAD patients from INTERMACS were compared with the 161 medical therapy patients from MedaMACS, all whom were Profile 4 to 7 at enrollment. There were some differences in baseline characteristics between patients enrolled in MedaMACS and patients enrolled in INTERMACS ([Table 1](#)). Most notably, there was a smaller proportion of women, a greater proportion of Profile 4 patients, lower HF medical therapy utilization, and worse baseline quality of life among INTERMACS patients. Interestingly, there were some markers of HF disease severity, including natriuretic peptide levels and renal function, that were actually worse among MedaMACS patients.

Actuarial survival by intention-to-treat analysis was not different between the medical therapy cohort from the MedaMACS study and the real-world LVAD therapy cohort from INTERMACS at 2 years ([Figure 3](#)). There was a

Table 3 Primary and Secondary End-points of the Entire MedaMACS Study Population at 1 Year

	MedaMACS study (N = 161)
Primary end-points	
Mortality	27 (17%)
LVAD received	13 (8%)
Transplant received	15 (9%)
Alive without LVAD or transplant ^a	88 (55%)
Unknown ^a	18 (11%)
Secondary end-points	
Inotropes required	22 (14%)
At least 1 rehospitalization	92 (57%)
Total number of rehospitalizations	1.7 ± 2.2

LVAD, left ventricular assist device; MedaMACS, Medical Arm of the Mechanically Assisted Circulatory Support.

^aEight patients withdrew consent; 10 patients transferred to centers not participating in MedaMACS.

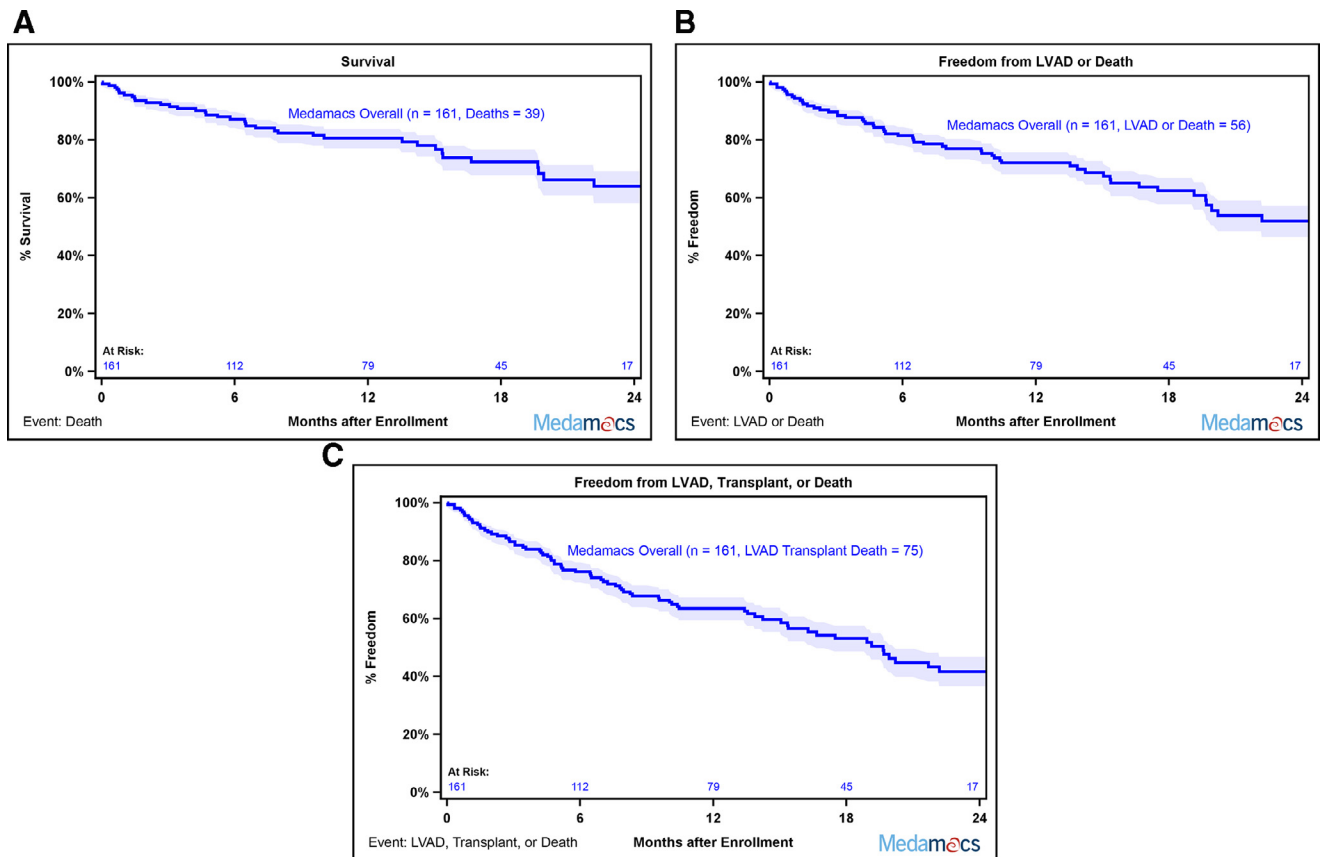


Figure 1 MedaMACS 2-year survival. (A) Kaplan–Meier survival of the entire MedaMACS cohort through 24 months of follow-up. The mortality rate was 17% at 1 year and 24% at 2 years after enrollment. Patients were censored at time of transplant, left ventricular assist device (LVAD) placement, or last follow-up. (B) Kaplan–Meier survival free of LVAD. The rate of death or LVAD placement was 35% at 2 years after enrollment. Patients were censored at time of transplant or last follow-up. (C) Kaplan–Meier survival free of LVAD or transplant. The rate of death, LVAD placement, or transplant was 47% at 2 years after enrollment. Patients were censored at time of last follow-up. Shaded areas represent 70% confidence intervals.

numeric trend toward less favorable outcomes with medical therapy at 24 months after enrollment in the overall cohort ($p = 0.0605$). Analysis stratified by individual INTERMACS profiles at enrollment showed a strong trend toward

better survival with LVAD therapy for Profiles 4 and 5 that did not reach statistical significance, with no differences in Profiles 6 and 7 (see [Figure S4](#) online). Analysis stratified by combining Profiles 4 and 5 showed that LVAD therapy

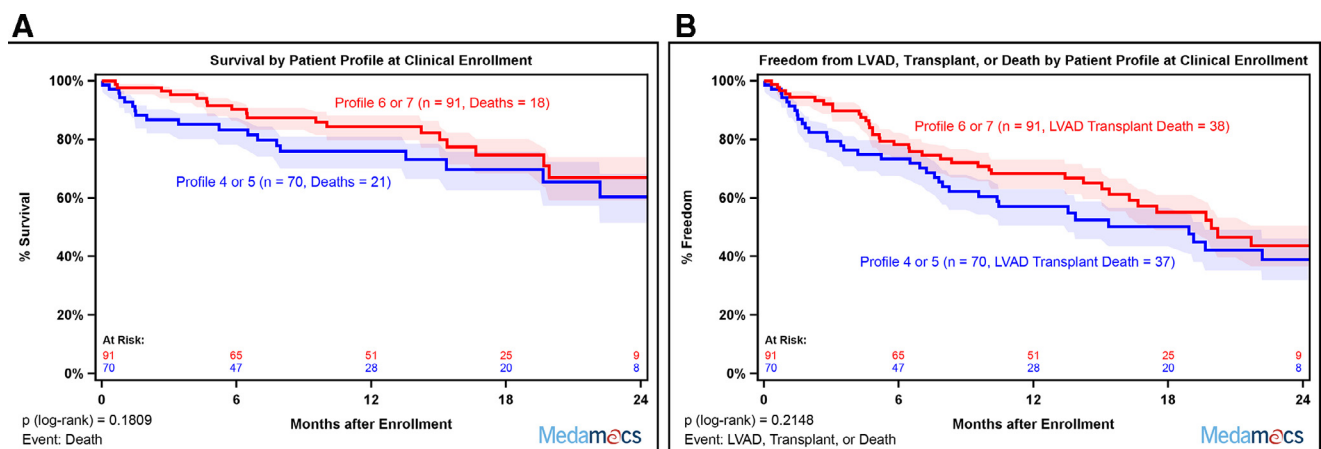


Figure 2 Two-year survival stratified by baseline INTERMACS patient profile. (A) Kaplan–Meier survival stratified by baseline patient profile was not statistically different. Patients were censored at time of transplant, left ventricular assist device (LVAD) placement, or last follow-up. (B) Kaplan–Meier survival free of LVAD or transplant stratified by baseline patient profile was not statistically different. Patients were censored at time of last follow-up. Patient Profiles 4 or 5 and 6 or 7 were combined for analysis. Shaded areas represent 70% confidence intervals.

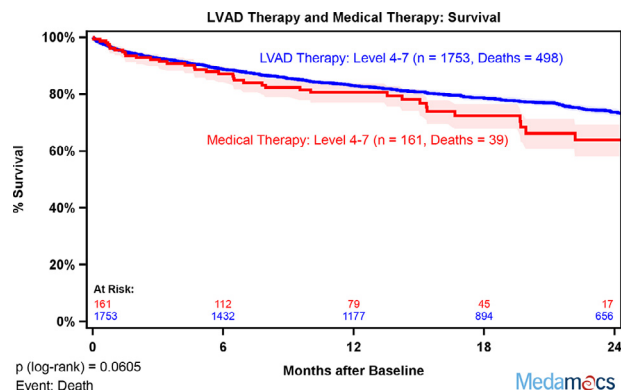


Figure 3 Intention-to-treat 2-year survival with medical vs left ventricular assist device (LVAD) therapy. Kaplan–Meier survival was equivalent with medical therapy (MedaMACS cohort) compared with LVAD therapy (INTERMACS cohort). Medical therapy patients were censored at time of transplant, ventricular assist device placement, or last follow-up. LVAD therapy patients were censored at recovery, transplant, or last follow-up. Shaded areas represent 70% confidence intervals.

was associated with better survival compared with medical therapy ($p = 0.0092$; Figure 4A). However, survival curves for survival with medical vs LVAD therapy were superimposable for Profiles 6 and 7 (Figure 4B).

Quality of life with medical vs LVAD therapy

Health-related quality of life, as assessed by the EuroQol VAS, was lower at baseline among patients receiving LVAD than those patients in whom medical therapy was continued, but it increased after 1 year for the survivors in both cohorts (Figure 5A). Specifically, the VAS score increased from 56 at baseline to 65 ($p = 0.007$) at 1 year in the medical therapy cohort. There was a larger increase in quality of life among LVAD therapy patients as the mean EuroQol VAS increased from 43 at baseline to 70 after 1 year of follow-up ($p < 0.0001$).

Survival with a good quality of life was defined as 1-year survival with EuroQol VAS score ≥ 50 and compared between the medical and LVAD cohorts. To account for bias that may result from patients who did not complete quality-of-life surveys, the results are presented as 3 groups for each cohort (alive with good quality of life [QoL], alive with poor QoL, alive—QoL info not completed) at 3 time-points (baseline, 6 months, and 1 year) as shown in Figure 5B. There was a decrease in the proportion of patients “alive with good QoL” from baseline (65%) to 1 year (22%) among medical therapy patients. By contrast, the proportion of patients “alive with good QoL” increased from 29% at baseline to 34% at 1 year among LVAD therapy patients.

Discussion

Ambulatory advanced HF patients at high risk for poor outcomes

The MedaMACS study is the largest prospective investigation to date of the trajectory for ambulatory patients on oral therapy with advanced systolic HF followed at centers also offering LVADs. The 161 total patients enrolled represented a real-world, diverse population of patients with advanced HF who were receiving contemporary medical and electrical therapies. Also, this is the largest population of these patients with predominantly INTERMACS Profiles 5 and 6, usually considered “less sick” or “too well” for mechanical circulatory support. In this entire ambulatory advanced HF cohort, 2-year event rates were striking, with 24% mortality, 11% VAD, 12% transplant, and only 53% alive on medical therapy. Given that only approximately half of the patients were alive on medical therapy without a transplant or VAD at 2 years, this suggests that HF patients similar to those enrolled in the MedaMACS study are at substantial risk for poor outcomes on continued medical therapy. The morbidity in this population was also high as

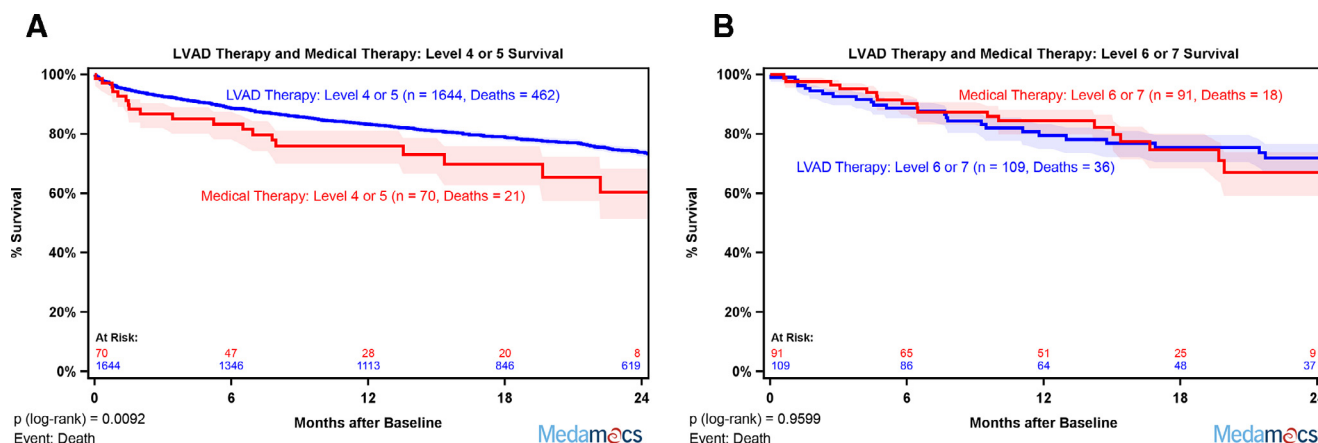


Figure 4 Two-year survival with medical vs left ventricular assist device (LVAD) therapy, stratified by patient profile at enrollment. (A) Kaplan–Meier survival suggested improved actuarial survival with LVAD vs medical therapy among Profile 4 or 5 patients. (B) Kaplan–Meier survival was equivalent for medical vs LVAD therapy among Profile 6 or 7 patients. Medical therapy patients were censored at time of transplant, LVAD placement, or last follow-up. LVAD therapy patients were censored at recovery, transplant, or last follow-up. Shaded areas represent 70% confidence intervals.

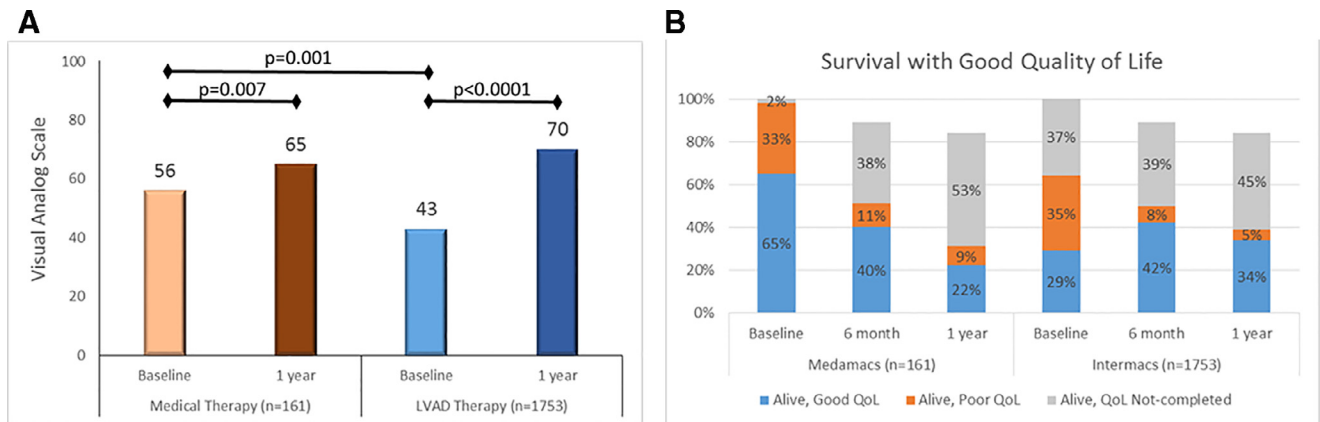


Figure 5 Quality of life and survival with medical vs left ventricular assist device (LVAD) therapy. (A) Health-related quality of life scores as measured by the EuroQoL Visual Analog Scale increased with both medical and LVAD therapy. (B) The proportion of patients alive with good quality of life decreased in the medical therapy arm, but increased in the LVAD therapy arm.

over half required another hospitalization, and many required multiple hospitalizations for HF. Given the high risk of failing oral medical therapies, ambulatory advanced HF patients, as described by the inclusion criteria for this study, should be considered for life-saving treatment for advanced heart failure such as cardiac transplantation and LVAD placement.

Medical vs LVAD therapy in ambulatory advanced HF

The comparison of medical therapy from the 161 patients enrolled in MedaMACS to LVAD therapy from the 1,753 patients in Profile 4 through 7 enrolled in the INTERMACS registry represents the single largest comparison of medical vs LVAD therapy in ambulatory advanced HF. There was no difference in intention-to-treat survival in medical vs LVAD therapy. However, the medical therapy patients who were in Profiles 4 and 5 appeared to be at exceptionally high risk for poor outcomes, and had better survival with LVAD therapy. This suggests that Profile 4 and 5 symptoms are a robust predictor of poor outcomes, and, as the event rate with medical therapy was so high in this cohort, strong consideration should be given to not delaying LVAD therapy in eligible patients who may benefit from current mechanical support devices under existing indications. In fact, as this was an intention-to-treat analysis where patients did cross over and receive transplants and LVADs, the analysis suggests there may be a mortality cost to delaying LVAD therapy among Profile 4 and 5 patients.

Among Profile 6 and 7 patients, given the equivalent survival with medical and LVAD therapy, additional considerations may be needed to guide whether a patient receives LVAD implantation or continues with medical therapy.¹² The adverse-event profile and rates of contemporary LVADs may influence patient decision-making, but could change with advancements in pump technology. Furthermore, the patient-reported outcome of health-related quality of life, as measured by EuroQoL VAS, improved with both medical and LVAD therapy, with a greater net increase

after LVAD therapy related to a lower baseline score. Future studies comparing medical therapy with LVAD in this less-sick advanced HF population should emphasize patient-reported outcomes to enhance shared decision-making about when to proceed with mechanical support.^{6,8,13}

MedaMACS confirms and extends the results of the ROADMAP study

The use of LVADs in non-inotrope-dependent advanced HF was studied recently in the Risk Assessment and Comparative Effectiveness of LVAD and Medical Management in Ambulatory HF Patients (ROADMAP) study, where intention-to-treat survival was identical for LVAD and medical therapy at 1 to 2 years of follow-up.^{14–16} The results of the MedaMACS study not only confirm some of the findings from the ROADMAP study, but extend the findings to a larger, real-world population (Table 4). In addition, the MedaMACS study included a higher proportion of INTERMACS patients in Profiles 5 to 7, which were previously not as well studied. As expected, with this shift toward less sick patients with an emphasis on Profiles 5 and 6, the overall mortality rate at 1 and 2 years was lower in the MedaMACS study than in the ROADMAP study. Although there was no intention-to-treat survival benefit for LVAD therapy in the ROADMAP study, the larger MedaMACS study suggests for the first time a mortality benefit for proceeding with LVAD therapy among Profile 4 and 5 patients and not waiting for clinical deterioration before implantation. An important caveat in the interpretation of both the MedaMACS and ROADMAP studies is that these non-randomized studies did not specifically require eligibility for LVAD, and thus included some patients with contraindications to LVAD therapy in the medical arm. The conditions that render patients less likely to be LVAD candidates may also render them at higher risk on medical therapy.⁷

Similar patterns for improvements in quality-of-life scores in both the medical and LVAD therapy arms were also observed in both the MedaMACS and ROADMAP studies. Such similar patterns of survival and quality of life

Table 4 Medical vs LVAD Therapy in Ambulatory Non-Inotrope-dependent Advanced Heart Failure^a

	MedaMACS (N = 161)	INTERMACS (N = 1,753)	ROADMAP medical therapy (N = 103)	ROADMAP LVAD therapy(N = 97)
Patient profile				
Profile 4	12%	80%	34%	65%
Profile 5	32%	13%	28%	22%
Profile 6	49%	4%	34%	10%
Profile 7	7%	3%	2%	0%
Outcome				
Death at 1 year	17%	16%	22%	20%
Death at 2 years	24%	28%	30%	26%

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; MedaMACS, Medical Arm of the Mechanically Assisted Circulatory Support; ROADMAP, Risk Assessment and Comparative Effectiveness of LVAD and Medical Management in Ambulatory HF Patients.

^aComparison of patient profiles at enrollment and raw mortality with medical therapy (MedaMACS), LVAD therapy (INTERMACS), and the medical and LVAD therapy groups of the ROADMAP study.^{14,15}

with medical and LVAD therapy highlight the need for end-points that integrate survival and robust assessments of patient-reported outcomes such as quality of life, particularly among Profile 6 and 7 patients. Survival end-points alone may not be adequate to distinguish meaningful outcomes between medical and LVAD therapy in an ambulatory population with advanced HF.¹⁷

Limitations

The results of this study should be interpreted in light of several limitations. First, the investigation was a registry-based comparison of medical vs LVAD therapy, and not a randomized, controlled trial. This introduces unmeasured confounding in comparison of the 2 cohorts, which are different as depicted by the baseline quality-of-life data. The patients included in the LVAD therapy arm were not propensity matched but rather included based on INTERMACS Profile 4 to 7 at enrollment, which has some subjectivity. Also, not all medical therapy patients completed 2 years of follow-up and these patients were censored at the time of last follow-up in a Kaplan–Meier analysis. Despite this reduction in statistical power, there were still differences detected between medical vs LVAD therapy. Furthermore, the survival analysis was intention-to-treat, and many of the medical therapy patients received a transplant or underwent LVAD implantation to prevent death during the study, so the benefit of these life-saving therapies was not fully captured in this analysis. In addition, LVAD recipients were inclusive of all INTERMACS centers, whereas medical participants were restricted to just 11 centers, which could limit the generalizability, but this was necessary as restriction to ambulatory patients in Profile 4 through 7 at the time of LVAD implantation would have resulted in too few patients had the analysis been restricted to just 11 centers. Event rates in the different INTERMACS profiles in the medical cohort should be interpreted within the context of study entry criteria, which mandated a recent HF hospitalization and other features defining an advanced stage of HF. Data regarding the reason for hospitalization or characteristics at the time of a study end-point was also

not captured. Finally, quality-of-life assessments were not completed by all patients. Despite these limitations, the MedaMACS study is the single largest published prospective outcome study of advanced HF patients on oral medical therapy and reflects real-world contemporary practice.

In conclusion, ambulatory patients with advanced HF in INTERMACS Profiles 4 through 7 who are receiving an initial strategy of oral medical therapy are at high risk for poor outcomes, including mortality and need for LVAD or transplantation. Only 53% of MedaMACS subjects were alive with ongoing medical therapy after 2 years of follow-up. As there are life-saving treatment options available for patients within this high-risk group, earlier referral to LVAD transplant centers for consideration of life-saving treatment options is needed so that patients may make well-informed decisions. Although overall 2-year survival for the entire cohort is similar with LVAD implantation and medical therapy, Profiles 4 and 5 can identify those patients with poor outcomes with medical therapy who may have better survival with LVAD therapy. Future studies should have a combined end-point that includes survival with a patient-centered outcome, such as quality of life, to better inform decisions about the timing of mechanical support before inotrope dependence.

Disclosure statement

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Supplementary materials

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