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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

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Short title: High Early Event Rate in Advanced HF

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Abstract

Background: The prognosis of ambulatory advanced heart failure (HF) patients who are not yet inotrope dependent and implications for evaluation and timing for transplant or destination therapy left ventricular assist device (DT-LVAD) are unknown. We hypothesized that the characteristics defining eligibility for advanced HF therapies will be a primary determinant of outcomes in these patients.

Methods: Ambulatory patients with advanced HF (NYHA class III-IV, INTERMACS profiles 4-7) were enrolled across 11 centers from 5/2013-2/2015. Patients were stratified into 3 groups: likely Transplant Eligible, DT-LVAD Eligible, and Ineligible for both Transplant and DT-LVAD. Clinical characteristics were collected and patients were prospectively followed for death, transplant, and LVAD implantation.

Results: A total of 144 patients were enrolled with a mean follow up of 10±6 months. Patients in the Ineligible cohort (n=43) had worse congestion, renal function, and anemia compared to Transplant (N=51) and DT-LVAD (N=50) Eligible patients. Ineligible patients had higher mortality (23.3% vs. 8.0% in DT-LVAD and 5.9% in Transplant, p=0.02). The differences in mortality were related to lower rates of transplantation (11.8% in Transplant vs. 2.0% in DT-LVAD and 0% in Ineligible, p=0.02) and LVAD implantation (15.7% in Transplant vs. 2.0% in DT-LVAD and 0% in Ineligible, p<0.01).

Conclusions: Ambulatory advanced HF patients who were deemed ineligible for transplant and DT-LVAD have markers of greater HF severity and a higher rate of mortality compared to transplant or DT-LVAD eligible patients. The high early event rate in this group emphasizes the need for timely evaluation and decision making regarding life-saving therapies.

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Keywords: mechanical support; ventricular assist device; cardiac transplantation; destination therapy; patient selection

Introduction

Morbidity and mortality for patients with advanced heart failure (HF) remain high. Cardiac transplantation has been the gold standard treatment for end-stage HF; however, the supply of donor hearts has been relatively static over the last two decades, limiting transplant to a very select few patients with few non-cardiac comorbidities.[1] Recent advances in mechanical circulatory support technology, specifically the use of durable continuous-flow left ventricular assist devices (LVADs), have offered an additional treatment option for HF patients. There are now over 2000 LVAD implants per year in the United States alone.[2] However, although LVADs can offer patients with advanced HF dramatic improvements in survival and quality of life, these devices carry a substantial risk of complications.[3] For this reason, developing evidence-based patient selection criteria for LVAD implant is paramount.

While the risk/benefit profile for LVAD in patients with inotrope dependent advanced HF—Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patient profiles 1-3 has been well studied, the prognosis of ambulatory patients who have advanced (HF) without inotropic therapy (INTERMACS profiles 4-7) is unknown and remains difficult to predict.[4-7] Furthermore, it is unclear if prognosis differs between patients eligible for transplant and/or destination therapy left ventricular assist device (DT-LVAD) and those ineligible for these therapies. We hypothesized that there may be differences in clinical characteristics and outcomes for patients with advanced HF based on their perceived candidacy for transplant versus DT-LVAD versus neither. Broader understanding of this patient population

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may help better direct the timing of transplant and DT-LVAD compared to medical therapy, and allow more appropriate comparisons between patients with and without mechanical support.

Methods

Patient Selection

Ambulatory patients with advanced HF (New York Heart Association class III-IV, INTERMACS profiles 4-7) were enrolled in the prospective, observational Medical Arm for Mechanically Assisted Circulatory Support (Medamacs) Registry across 11 advanced HF-transplant cardiology centers from May 1, 2013 to February 28, 2015. Patient inclusion and exclusion criteria are provided in Figure 1. This Medamacs Registry study is a larger and distinct study that followed the initial screening pilot Medamacs feasibility study that enrolled patients in a smaller group of centers between October 2010 and April 2011.[8] 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.

At the time of enrollment, the treating HF clinician was asked to determine the patient's likelihood of being eligible for transplant or LVAD, indicating whether the patient was (1) likely Transplant Eligible (also presumed eligible for a LVAD), (2) likely DT-LVAD Eligible (but uncertain or unlikely to be eligible for transplant), or (3) uncertain or likely Transplant and DT-LVAD Ineligible. Respondents were meant to use clinical judgment to discern among the three categories and only one selection was allowed for each study participant. This information was collected on every patient enrolled in the Medamacs Registry. Perceived barriers to transplant or DT-LVAD ineligible were also recorded for all patients. For this analysis, each patient was

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stratified into one of these three cohorts based on this initial assessment of potential eligibility for advanced HF therapies.

Outcome Measures

Data were prospectively collected for patients over a pre-specified 24 month follow up period. This report was an interim analysis of this ongoing observational study. Demographics, clinical characteristics, laboratory, echocardiography, hemodynamic, and functional status data were collected in addition to quality of life surveys at the time of enrollment. These measures were reassessed in addition to collection of interval events at 1 month, 1 year, and 2 years after entry into the study. Since the proportion of patients too sick for the six minute walk and gait speed tests to be administered can vary over time between the groups and potentially bias the comparisons, patients unable to complete these assessments had a value of 0 assigned to these measures as in previous analyzes.[9] Additional phone calls to measure interval events were made at 6 and 18 month time intervals.

Additional clinical determinations were assessed at enrollment as well. In addition to judging eligibility for advanced therapies, the treating HF clinician also identified perceived comorbid concerns and contraindications to transplant and/or DT-LVAD. Outcomes measures were prospectively collected at the time of occurrence and included hospitalization, stroke, transplant, mechanical circulatory support, inotrope utilization, and death.

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Statistical Analysis

All statistical analyses were preformed centrally at the University of Alabama at Birmingham Data and Clinical Coordinating Center. Data were reported as mean values ± standard deviations or count (percentage). Univariate comparisons between the cohorts of patients based on differing eligibility were performed using the chi-square test of Fisher's exact test for categorical variables and the one-way ANOVA test for continuous variables. A two-tailed P value of <0.05 was considered statistically significant. Kaplan-Meier survival curves and log rank tests were used to demonstrate unadjusted survival differences among the 3 study cohorts. SAS 9.4 statistical software (Cary, NC) was used for all statistical analysis.

Results

A total of 144 eligible patients were enrolled between May 1, 2013 and February 28, 2015 with an average follow up of 10 ± 6 months. Of these 144 patients, HF clinicians identified 51 patients who were likely Transplant Eligible, 50 patients who were likely DT-LVAD Eligible (but unlikely to be transplant eligible), and 43 patients who were likely Transplant/DT-LVAD Ineligible. Fifty seven (39.6%) of the 144 patients were specifically referred to the enrolling advanced HF program for evaluation for cardiac transplant and/or LVAD, and 34 (23.6%) patients had completed a formal transplant and/or LVAD evaluation prior to enrollment in Medamacs.

As expected, Transplant Eligible patients were younger than DT-LVAD Eligible and Transplant/DT-LVAD Ineligible patients (Table 1). Transplant and DT-LVAD Eligible patients were more likely to be Caucasian and Transplant Eligible were more likely to have post high school education. INTERMACS patient profiles and inotrope utilization in the preceding 6

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months prior to enrollment were similar among the 3 cohorts at the time of enrollment with Transplant Eligible having a modestly lower number of cardiac hospitalizations in the preceding 12 months. Cardiac medication utilization was generally similar among the 3 cohorts at the time of enrollment with the exception of less utilization of hydralazine/nitrates in Transplant Eligible (perhaps related to differences in racial background among the cohorts) and less utilization of aldosterone antagonists in Transplant/DT-LVAD Ineligible (perhaps related to differences in renal function).

Transplant/DT-LVAD Ineligible patients had some traditional predictors of greater HF disease severity at the time of enrollment including worse renal function, evidence of greater congestion based on natriuretic peptide levels and hemodynamics measurements, more severe anemia, and worse functional status based on six minute walk distance (Table 2). As expected, Transplant/DT-LVAD Ineligible patients had more perceived concerns and contraindications to advanced HF therapies at the time of enrollment (Table 3). Some of these perceived contraindications were related to the traditional predictors of greater HF disease severity such as advanced age, renal dysfunction, malnutrition/cachexia, and pulmonary hypertension. Other contraindications less commonly reflected in most HF prognosis models were also identified– including perceived frailty, limited social support, and repeated non-compliance.

The overall event rate in the entire study population was high during an average follow up period of slightly less than 10 months. Of the total study population of 144 patients, 75.7% were alive without a transplant or LVAD, 11.8% had died, 4.9% received a transplant, and 6.3% had a LVAD implantation. The high mortality rates were driven by patients that were Transplant/DT-LVAD Ineligible (Figure 2). Transplant/DT-LVAD Ineligible patients had substantially higher mortality rates (23.3% vs. 8.0% in DT-LVAD Eligible and 5.9% in

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Transplant Eligible, p=0.02). There was also a trend towards greater morbidity among Ineligible patients with a higher portion, but not statistically significant, number of patients requiring inotropes, higher rates of rehospitalization, and greater number of rehospitalizations (Table 4).

Much of the reduction in mortality rates among Transplant Eligible and DT-LVAD Eligible patients may have been related to the utilization of advanced HF therapies in these groups (Table 4). Transplant Eligible patients were more likely to have received a transplant (11.8% vs. 2.0% in DT-LVAD Eligible and 0% in Transplant/DT-LVAD Ineligible, p=0.02). In addition, Transplant Eligible patients were more likely to have received a LVAD (15.7% vs. 2.0% in DT-LVAD Eligible and 0% in Transplant/DT-LVAD Ineligible, p<0.01). The overall survival free from transplant or LVAD among DT-LVAD Eligible patients was actually the highest among the groups and the lowest among Transplant Eligible patients (Figure 3).

Discussion

Among ambulatory advanced HF patients not dependent on inotropes, patients who were felt to be ineligible for Transplant/DT-LVAD had markers of greater HF disease severity and had worse outcomes compared to those thought to be Transplant and DT-LVAD Eligible. The high mortality rate of 23.3% among likely Ineligible patients after an average follow up period of just 10 months would suggest that this is a very high risk group of patients with poor prognosis without life-saving advanced HF therapies. Despite this poor prognosis, only 30% of patients in this group had undergone a formal evaluation for transplant and/or LVAD at the time of enrollment in Medamacs. Such timely evaluations and discussions of prognosis and options is an important part of shared decision making in regards to advanced HF therapies.[10]

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The somewhat low rates of formal evaluation for transplant and/or LVAD despite the high rates of mortality, transplant, and LVAD implantation in all cohorts is particularly interesting given the nature of the Medamacs study and the participating centers. Patients were enrolled during a contemporary period of time in major medical centers with experienced advanced HF programs well versed in the indications, evaluation, and timing of cardiac transplantation and LVAD implantation. This illustrates the complex nature and limitations of predicting prognosis and survival in HF patients even among clinicians and care teams with considerable experience in the care of this advanced HF patient population.

The limitations of HF prognostic models are further highlighted by results from this study and the possibilities of using additional non-traditional markers of poor prognosis in HF to avoid underestimating outcomes.[4-7] In addition to having worse traditional markers of HF disease severity, HF clinician identified frailty, nonadherence, and limited social support were more common among Transplant/DT-LVAD Ineligible patients and each adversely effects outcomes in HF patients.[11-15] The use of these factors in combination with other traditional risk factors warrants further investigation as they are not currently part of HF risk stratification or transplant and LVAD selection models, but clearly seem to be associated with poorer prognosis.[16]

Physician identified frailty but not gait speed appears to be associated with higher mortality in this study. Frailty is generally determined in two ways: the "frailty phenotype" using a small number of directly assessed measures[17] or by a "frailty index" using a larger set of data including components of history, examination, comorbidities, and lab variables.[18] Gait speed, the most well-studied of the five criteria in the frailty phenotype, was not different in our three groups of patients. This is surprising as gait speed alone has been shown to be an excellent predictor of outcomes in cardiovascular patients.[19] However, given the excess number of

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comorbid conditions among the Transplant/DT-LVAD Ineligible cohort, it is possible that the astute clinicians enrolling patients in this study subconsciously assessed a "frailty index."[13]

Another important and somewhat paradoxical observation from this study is the fact that Transplant Eligible patients had the lowest event-free survival without transplant or LVAD placement. This was contrasted by DT-LVAD eligible patients having the best event-free survival without transplant or LVAD. The reasons for these differences are not fully explained by this study as we did not collect information regarding listing status (1A, 1B, or 2) at the time of transplant, accrued transplant list wait time, regional heterogeneity in donor availability, INTERMACS profiles at time of transplant/LVAD, or the need for urgent LVAD. However, the fact that Transplant Eligible patients had the highest rate of LVAD implantation in our cohort certainly does bring into question current donor heart allocation policies and the increasing utilization of LVADs as a bridge to transplantation.[20] It is possible that the high rate of LVAD placement among Transplant Eligible patients reflects clinicians' willingness to move towards earlier LVAD placement in patients listed for transplant in order to upgrade their transplant listing priority and ultimately facilitate the desired goal of transplantation. By contrast, clinicians may be willing to continue medical treatment in DT-LVAD eligible patients where transplantation is not the end-goal. Further research regarding potential alterations in patient selection and LVAD utilization related to donor heart allocation policies are needed in order to ensure optimal care.

Finally, it is important to note that as there are differences in baseline characteristics and outcomes based on eligibility for advanced HF therapies; future studies comparing LVADs to medical therapy should, in theory, carefully select patients that are only eligible for transplant and/or DT LVAD to allow for more accurate comparisons. Caution should be used if using non-

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randomized studies or registry databases that may compare patients who received a LVAD to a group of patients who were treated with medical therapy, if many of the patients in the medical therapy cohort would have been ineligible for a LVAD in the first place. For example in the ROADMAP Study, study physicians chose to assign patients to the optimal medical management arm for two reasons that are likely the equivalent of ineligibility for LVAD therapy in our study—specifically the patient not being a good surgical candidate (14%) and "other" including substance abuse, financial, and compliance concerns (9%).[21] It is possible that such ineligible patients that end up in a medical therapy arm of a study may be quite different than those eligible patients that end up in a LVAD therapy arm, making it difficult to tease out the driving factor (LVAD vs. intrinsic patient characteristics) between potential differences in study outcomes.

Limitations

A major limitation of this study is that the definitions of eligibility from one center's LVAD and transplant program may not be the same. In addition, the perceived concerns and contraindications to LVAD and transplant at the time of enrollment did not have standard definitions, but rather reflected the HF clinicians' clinical judgement when the patient entered the study. However, this was a prospective registry study from multiple centers with established LVAD and transplant programs so at least reflects current practice. The categorization of patients based on eligibility for transplant and LVAD was based on HF clinician assessment at the time of enrollment, and obviously this can change as well. Given the high event rate early after enrollment, the results of this study would suggest that initial decisions on candidacy may still be important given the rapid clinical decline of some patients.

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Conclusions

Among a group of ambulatory advanced HF patients on oral medication therapy, the overall survival rate without transplant or LVAD in the entire study population after a follow up period of slightly less than 10 months was approximately 75%—suggesting that HF patients with similar characteristics to those enrolled in the Medamacs Registry are a group at particularly high risk for poor outcomes and warrant referral to centers for consideration of advanced HF therapies. There are differences in baseline patient and clinical characteristics and outcomes depending on eligibility for transplant and/or LVAD. Patient who were likely ineligible for transplant or DT-LVAD had some traditional markers of greater HF disease severity (higher filling pressures and natriuretic peptide levels with worse renal function and anemia) and a greater number of clinician perceived contraindications to advanced HF therapies that are not traditionally captured in HF prognostic models such as limited social support, non-compliance, and frailty. The higher rate of early mortality in this cohort compared to patients considered likely transplant and/or LVAD eligible emphasizes the need for timely evaluation and decision making regarding life-saving advanced HF therapies or early referral to palliative care.

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Conflict of Interest Disclosures

Dr. DeVore reports receiving research support from the American Heart Association, Amgen, Maquet, Novartis, and Thoratec and consulting with Maquet. Dr. Teuteberg reports receiving advertising board and speaking honoraria from HeartWare, Abiomed, and CareDx as well as receiving support from Thoratec and Sunshine Heart. Mr. Cantor reports receiving support from Sunshine Heart. The remaining authors have no disclosures.

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Figure 1: Medamacs Registry patient inclusion and exclusion criteria

Inclusion Criteria

1. Age 18-80 years
2. NYHA class III-IV heart failure for 45 of the last 60 days
3. Left ventricular ejection fraction ≤ 35%
4. Heart failure diagnosis or typical symptoms for 12 months
5. Use of evidence based oral medications (beta-blockers, ACE-inhibitors/ARBs, aldosterone antagonist) for at least 3 months prior to enrollment or documented medication contraindication or intolerance.
6. Hospitalization for heart failure within the previous 12 months (other than for elective procedure)

In addition, they must have at least one of the following:

A. An additional unplanned hospitalization during the previous 12 months for a total of at least 2 inpatient hospitalizations lasting >24 hours with heart failure as the primary or secondary diagnosis within the previous 12 months

OR

B. (Any one of these)

1) Peak oxygen uptake (VO2) <55% of age- and sex-predicted (using Wasserman equation) OR a peak VO2 ≤16 ml/kg/min for men and ≤14 ml/kg/min for women in a test with an RER >1.08 on cardiopulmonary exercise testing.
2) 6-minute walk distance <300 meters without non-cardiac limitation.
3) Serum BNP > 1000 pg/ml (NT-proBNP > 4000 pg/ml) as outpatient or at hospital discharge.

OR

C. Seattle Heart Failure Model Score > 1.5.

Exclusion Criteria

1. Age >80 years or <18 years
2. Non-cardiac diagnosis anticipated to limit 2-year survival (≥30-50% mortality within 2 years from non-cardiac diagnosis)
3. Primary functional limitation from non-cardiac diagnosis even if not likely to limit survival
4. QRS > 120msec and planned biventricular pacemaker implant or biventricular pacemaker implantation within past 90 days
5. Current home intravenous inotrope therapy
6. Chronic hemodialysis or peritoneal dialysis
7. Scheduled for non-ventricular assist device cardiac surgery on current hospital admission
8. Obvious anatomical or other major contra-indication to any cardiac surgery in the future (e.g. previous pneumonectomy, advanced connective tissue disease)
9. Actively listed for heart transplant as UNOS Status 1 or 2
10. History of cardiac amyloidosis
11. Dominant lesion of at least moderate aortic or mitral stenosis or congenital structural heart defect.

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Figure 2: Unadjusted survival among Medamacs Registry patients based on eligibility for Transplant and DT-LVAD. Patients were censored at time of transplant or ventricular assist device placement. Transplant/DT-LVAD Ineligible patients had lower survival compared to the other cohorts. Error bars represent 70% confidence intervals.

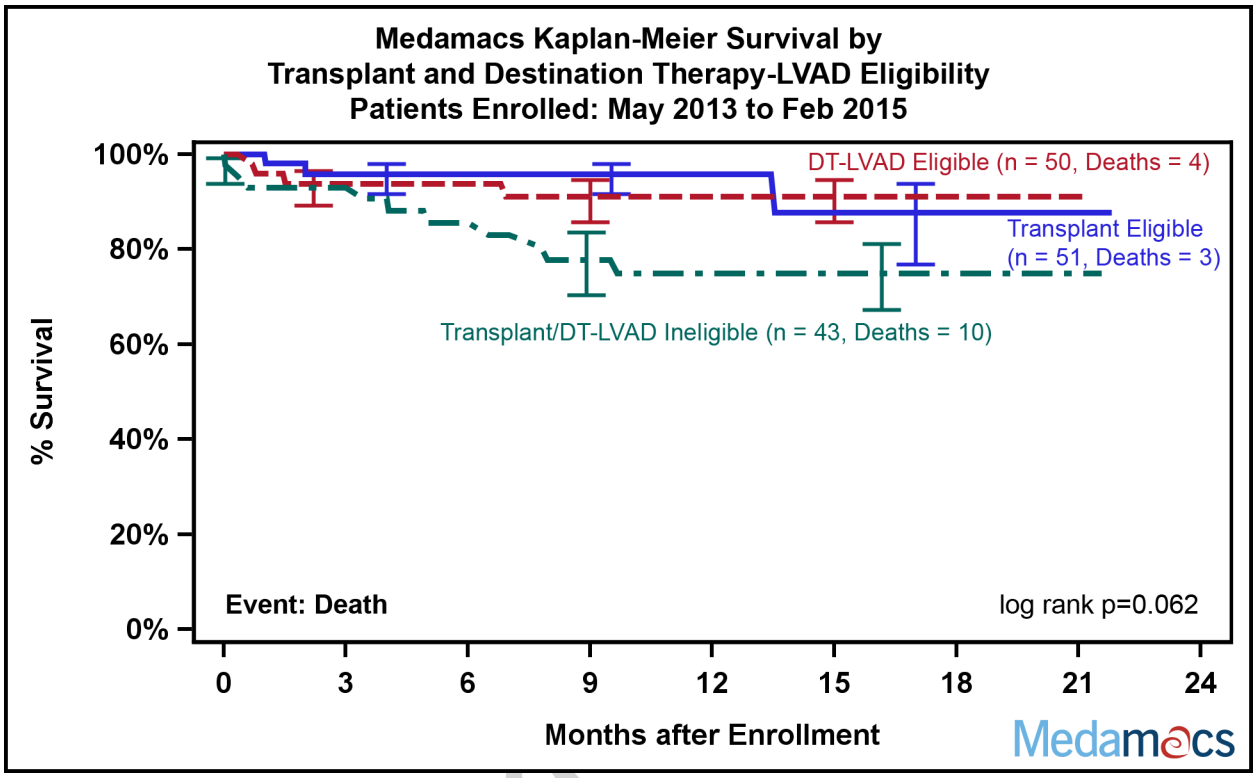

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Figure 3: Unadjusted survival without transplant or ventricular assist device (VAD) placement among Medamacs Registry patients based on eligibility for Transplant and DT-LVAD. DT-LVAD Eligible patients had the best survival free from transplant or VAD while Transplant Eligible patients had the lowest survival free from transplant or VAD. Error bars represent 70% confidence intervals.

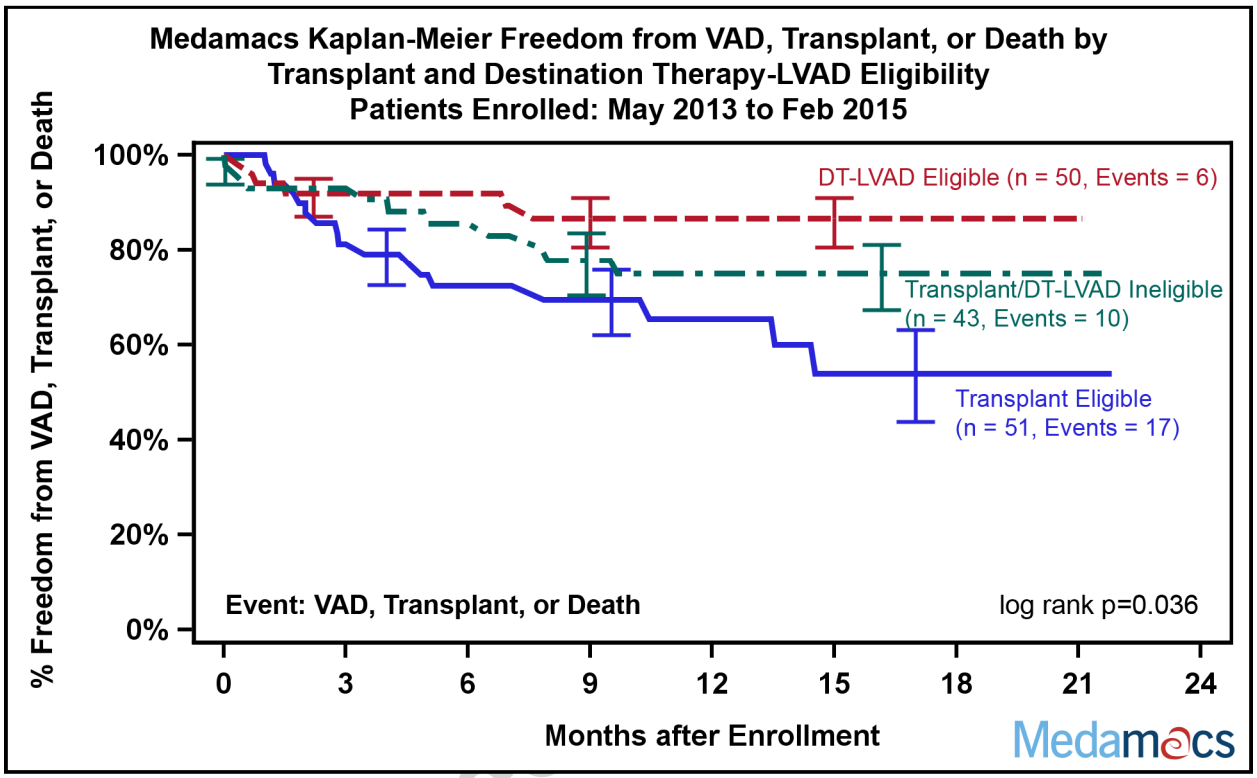

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Table 1. Baseline Patient Characteristics

	Transplant Eligible (N=51)	DT-LVAD Eligible (N=50)	Transplant/ DT-LVAD Ineligible (N=43)	P value
Demographics				
Age (years)	54.5 ± 9.9	61.3 ± 11.7	59.8 ± 11.3	<0.01
Male gender	33 (65%)	36 (72%)	28 (65%)	0.69
Race				0.02
African-American	12 (24%)	11 (22%)	21 (49%)	
Caucasian	37 (72%)	38 (76%)	21 (49%)	
Other	2 (4%)	1 (2%)	1 (2%)	
Married or domestic partnership	32 (65%)	30 (60%)	23 (55%)	0.59
Post high school education	30 (81%)	16 (47%)	17 (59%)	0.01
Heart Failure Characteristics				
Etiology of heart failure				0.09
Ischemic cardiomyopathy	12 (24%)	21 (42%)	18 (42%)	
Idiopathic dilated cardiomyopathy	23 (45%)	18 (36%)	20 (46%)	
Other etiology	16 (31%)	11 (22%)	5 (12%)	
Implantable cardioverter defibrillator Present	43 (84%)	44 (88%)	33 (77%)	0.34
Cardiac resynchronization therapy Present	12 (24%)	21 (42%)	9 (22%)	0.06
INTERMACS Patient Profile				0.26
4-Resting Symptoms	3 (6%)	8 (16%)	6 (14%)	
5-Exertion Intolerant	12 (23%)	19 (38%)	12 (28%)	
6-Exertion Limited	29 (57%)	20 (40%)	22 (51%)	
7-Advanced NYHA Class 3	7 (14%)	3 (6%)	3 (7%)	
Inotrope therapy required in preceding 6 months	10 (21%)	7 (15%)	9 (21%)	0.65
Number of cardiac hospitalizations in preceding 12 months				<0.01
One	22 (44%)	7 (14%)	11 (26%)	
Two	14 (28%)	25 (50%)	15 (36%)	
Three	9 (18%)	4 (8%)	9 (21%)	
Four or more	5 (10%)	14 (28%)	7 (17%)	
Prior transplant and/or DT-LVAD Evaluation	11 (21.6%)	10 (20%)	13 (30%)	0.47
Reason for initial referral to advanced HF program				0.33
Cardiac transplant and/or DT-LVAD Evaluation	26 (51%)	20 (40%)	11 (25%)	
Evaluation of severe heart failure	15 (29%)	20 (40%)	21 (49%)	

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New diagnosis heart failure within same institution	4 (8%)	4 (8%)	5 (12%)	
Unknown	6 (12%)	6 (12%)	6 (14%)	
Medication usage at the time of enrollment				
ACEI or ARB	37 (73%)	30 (60%)	21 (49%)	0.06
Beta-blockers	45 (88%)	47 (94%)	36 (84%)	0.29
Aldosterone antagonist	39 (77%)	33 (66%)	21 (49%)	0.02
Loop diuretics	48 (94%)	46 (94%)	41 (95%)	0.95
Digoxin	23 (45%)	25 (50%)	19 (44%)	0.83
Hydralazine	9 (18%)	18 (36%)	16 (37%)	0.06
Nitrate	9 (18%)	20 (40%)	15 (35%)	0.04
Warfarin	23 (45%)	19 (38%)	20 (47%)	0.66
Aspirin	27 (53%)	32 (64%)	27 (63%)	0.47
Statin	20 (39%)	32 (64%)	23 (54%)	0.04

INTERMACS=Interagency Registry for Mechanically Assisted Circulatory Support, NYHA=New York Heart Association, DT-LVAD=Destination Therapy Left Ventricular Assist Device, ACEI=Angiotensin Converting Enzyme Inhibitor, ARB=Angiotensin Receptor Blocker

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Table 2. Clinical characteristics at the time of enrollment in the Medamacs Study

	Transplant Eligible	DT-LVAD Eligible	Transplant/ DT-LVAD Ineligible	P value
Vital Signs				
Weight (kg)	88 ± 25	100 ± 25	91 ± 26	0.04
Height (cm)	172 ± 13	174 ± 10	170 ± 11	0.27
Body Mass Index (kg/m^2)	30 ± 9	33 ± 9	31 ± 8	0.11
Heart rate (beats per minute)	79 ± 14	79 ± 14	80 ± 16	0.95
Systolic blood pressure (mmHg)	106 ± 14	114 ± 15	112 ± 17	0.03
Diastolic blood pressure (mmHg)	68 ± 10	68 ± 9	70 ± 13	0.65
Laboratory Values				
Sodium (mmol/L)	137 ± 4	138 ± 3	137 ± 4	0.36
Potassium (mEq/L)	4.1 ± 0.5	4.1 ± 0.5	4.2 ± 0.5	0.70
Blood urea nitrogen (mg/dL)	31 ± 13	33 ± 18	40 ± 28	0.09
Creatinine (mg/dL)	1.4 ± 0.4	1.4 ± 0.5	1.7 ± 0.8	<0.01
Alanine aminotransferase (u/L)	46 ± 53	35 ± 50	23 ± 15	0.09
Aspartate aminotransferase (u/L)	37 ± 17	34 ± 36	29 ± 13	0.37
Total bilirubin (mg/dL)	1.5 ± 0.9	1.0 ± 0.6	0.9 ± 0.5	<0.01
NT-pro B-type natriuretic peptide (pg/ml)	3007 ± 3002	3963 ± 3276	7986 ± 4970	<0.01
Albumin (g/dL)	3.9 ± 0.5	3.8 ± 0.7	3.7 ± 0.6	0.18
Pre-albumin (mg/dL)	20 ± 8	20 ± 7	23 ± 12	0.70
Total cholesterol (mg/dL)	136 ± 40	126 ± 35	133 ± 55	0.68
Uric acid (mg/dl)	9.0 ± 2.9	8.8 ± 2.6	13.5 ± 12.6	0.11
White blood cell count (K/uL)	7.0 ± 2.2	7.5 ± 2.5	6.8 ± 2.4	0.34
Hemoglobin (g/dl)	13.7 ± 2.2	12.8 ± 2.6	11.7 ± 2.1	<0.01
Hematocrit (%)	42 ± 6	39 ± 7	36 ± 6	<0.01
Platelets (K/uL)	202 ± 63	218 ± 83	231 ± 80	0.22
International normalized ratio	1.6 ± 0.7	1.5 ± 0.7	1.8 ± 0.9	0.23
Lymphocyte (%)	23 ± 9	21 ± 9	20 ± 9	0.36
Baseline Exercise Testing and Functional Status				
Six Minute Walk (meters)	255 ± 141	162 ± 142	176 ± 159	0.01
Gait speed (meters/second)	0.9 ± 0.5	0.6 ± 0.5	0.7 ± 0.6	0.08
Peak oxygen uptake VO2 (mL/kg/min)	12.7 ± 5.6	11.7 ± 4.7	12.0 ± 1.1	0.87
Peak oxygen uptake (%) predicted	40 ± 14	41 ± 10	52 ± 12	0.27
Ventilatory efficiency (VE/VCO2)	36 ± 11	38 ± 8	36 ± 5	0.83
Peak respiratory exchange ratio	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	0.76
Echocardiographic and Right Heart Catheterization Hemodynamic Data				
Left ventricular ejection fraction (%)	20 ± 7	21 ± 6	22 ± 6	0.36

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LV dimension diastole (cm)	6.5 ± 1.0	6.6 ± 0.8	6.4 ± 0.8	0.71
Right atrial pressure (mmHg)	11 ± 7	11 ± 5	13 ± 7	0.40
Pulmonary artery systolic pressure (mmHg)	46 ± 13	53 ± 13	54 ± 13	0.03
Pulmonary artery diastolic pressure (mmHg)	23 ± 7	24 ± 8	27 ± 8	0.13
Pulmonary wedge pressure (mmHg)	17 ± 7	23 ± 8	23 ± 9	<0.01
Cardiac output (L/min)	4.2 ± 1.4	4.8 ± 1.4	4.7 ± 1.6	0.23
Cardiac index (L/min/m^2)	2.2 ± 0.8	2.2 ± 0.6	2.2 ± 0.6	0.95

Table 3. Perceived comorbid concerns and contraindications to Transplant or DT LVAD at the time of enrollment

	Transplant Eligible	**DT-LVAD Eligible**	**Transplant/ DT-LVAD Ineligible**	**P value**
Comorbid Concerns to Transplant or DT-LVAD				
Advanced Age	2 (4%)	11 (22%)	7 (16%)	0.03
Diabetes	2 (4%)	8 (16%)	4 (9%)	0.12
Frailty	1 (2%)	7 (14%)	9 (21%)	0.01
History of gastrointestinal ulcers	1 (2%)	2 (4%)	3 (7%)	0.44
Major stroke	4 (8%)	2 (4%)	4 (9%)	0.60
Malnutrition/cachexia	3 (6%)	0 (0%)	5 (12%)	0.03
Musculoskeletal limitations	2 (4%)	8 (16%)	8 (19%)	0.07
Peripheral vascular disease	3 (6%)	5 (10%)	2 (5%)	0.66
Pulmonary disease	11 (22%)	16 (32%)	10 (23%)	0.44
Pulmonary hypertension	16 (31%)	16 (32%)	16 (37%)	0.81
Psychiatric disorder	1 (2%)	1 (2%)	1 (2%)	0.99
Obesity	15 (29%)	20 (40%)	15 (35%)	0.54
Risk of recurrent infection	0 (0%)	0 (0%)	2 (5)	0.09
Renal dysfunction	18 (35%)	25 (50%)	22 (51%)	0.21
Currently smoking	2 (4%)	2 (4%)	1 (2%)	0.99
History of smoking	20 (39%)	24 (48%)	8 (19%)	0.01
History of alcohol abuse	3 (6%)	3 (6%)	2 (5%)	0.99
History of illicit drug use	1 (2%)	5 (10%)	2 (5%)	0.19
Limited social support	2 (4%)	6 (12%)	11 (26%)	<0.01
Limited cognition/understanding	1 (2%)	1 (2%)	4 (9%)	0.24
Repeated non-compliance	3 (6%)	7 (14%)	8 (19%)	0.16
Total Number of Concerns	3.1 ± 2.1	4.1 ± 3.0	4.5 ± 3.3	0.04
Comorbid Contraindication to Transplant or DT-LVAD				
Advanced Age	0 (0%)	8 (16%)	7 (16%)	0.01

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Diabetes	2 (4%)	6 (12%)	3 (7%)	0.30
Frailty	0 (0%)	4 (8%)	7 (16%)	<0.01
History of gastrointestinal ulcers	0 (0%)	0 (0%)	2 (5%)	0.09
Major stroke	0 (0%)	0 (0%)	1 (2%)	0.31
Malnutrition/cachexia	0 (0%)	0 (0%)	3 (7%)	0.02
Musculoskeletal limitations	2 (4%)	2 (4%)	5 (12%)	0.29
Peripheral vascular disease	1 (2%)	1 (2%)	0 (0%)	0.99
Pulmonary disease	0 (0%)	2 (4%)	3 (7%)	0.18
Pulmonary hypertension	3 (6%)	1 (2%)	7 (16%)	0.03
Psychiatric disorder	0 (0%)	1 (2%)	1 (2%)	0.54
Obesity	8 (16%)	13 (26%)	11 (26%)	0.38
Risk of recurrent infection	0 (0%)	0 (0%)	2 (5%)	0.09
Renal dysfunction	2 (4%)	4 (8%)	11 (26%)	<0.01
Currently smoking	1 (2%)	2 (4%)	1 (2%)	0.84
History of smoking	2 (4%)	6 (12%)	0 (0%)	0.04
History of alcohol abuse	0 (0%)	0 (0%)	1 (2%)	0.30
History of illicit drug use	0 (0%)	1 (2%)	1 (2%)	0.54
Limited social support	0 (0%)	4 (8%)	10 (23%)	<0.01
Limited cognition/understanding	0 (0%)	1 (2%)	2 (5%)	0.20
Repeated non-compliance	1 (2%)	5 (10%)	8 (19%)	0.02
Total Number of Contraindications	0.5 ± 1.0	1.4 ± 1.3	2.2 ± 1.8	<0.01

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Table 4. Clinical outcomes based on the likely eligibility for transplant and/or LVAD.

	Transplant Eligible	DT-LVAD Eligible	Transplant/ DT-LVAD Ineligible	P value
Clinical Outcomes				
Survival Outcomes				
Mortality	3 (6%)	4 (8%)	10 (23%)	0.02
Ventricular assist device received	8 (16%)	1 (2%)	0 (0%)	<0.01
Transplant received	6 (12%)	1 (2%)	0 (0%)	0.02
Alive without LVAD or Transplant	33 (65%)	43 (86%)	33 (77%)	0.04
Inotropes required	3 (6%)	3 (6%)	6 (14%)	0.31
At least one rehospitalization	9 (18%)	11 (22%)	14 (33%)	0.22
Total Number of Rehospitalizations	0.7 ± 1.2	0.7 ± 1.2	1.5 ± 2.0	0.09

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