Outcomes in Advanced Heart Failure Patients with Left Ventricular Assist Devices for Destination Therapy

Park et al: HeartMate II for Destination Therapy

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Journal Subject Codes: Cardio-renal physiology/ pathophysiology, Congestive, Other heart failure, Other Treatment
Abstract

Background—The HeartMate II (HMII) Destination Therapy (DT) trial demonstrated significant improvements in outcomes in continuous-flow LVADs compared to patients implanted with the pulsatile-flow HeartMate XVE. The primary hypothesis of the current study is that trial patients enrolled after the initial data cohort would have better clinical outcomes.

Methods and Results—Two hundred eighty one patients who underwent HMII for DT from May 2007 – March 2009 (Mid Trial (MT) group) were compared to the initial 133 HMII patients from March 2005 – May 2007 (Early Trial (ET) group). Patient entry criteria were the same during the two time periods. Survival, adverse events, and quality of life (QOL) were compared between the two groups. Baseline characteristics were similar between the groups. Compared to the ET group, patients in the MT group had reduced adverse event rates for bleeding requiring transfusions (1.66 vs. 1.13 events/pt-yr, \( p<0.001 \)), sepsis (0.38 vs. 0.27, \( p=0.025 \)), device-related infections (0.47 vs. 0.27, \( p<0.001 \)), and hemorrhagic stroke (0.07 vs. 0.03, \( p=0.01 \)). Other event rates were similar between groups including ischemic stroke (0.06 vs. 0.05 events/pt-yr, \( p=0.57 \)). Survival at 1 year in the MT group was 73\% vs. 68\% in the ET group (\( p=0.21 \)). Additionally, there was a significant reduction in deaths due to hemorrhagic stroke (\( p=0.01 \)). QOL improvements were significant in both the groups (\( p<0.001 \)).

Conclusions—The benefit of DT therapy with the HM II is confirmed in subsequent trial patients, with improved adverse event rates and a strong trend for improvements in survival.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00121485.

Key Words: heart failure; mechanical circulatory support; ventricular assist device; HeartMate II
Abbreviations

CF – Continuous Flow
LVAD – left ventricular assist device
MCS – mechanical circulatory support
FDA – Food and Drug Administration
NYHA – New York Heart Association
HMII - HeartMate II
CAP - Continued Access Protocol
BTT: Bridge to Transplantation
DT: Destination Therapy
6MWD – Six Minute Walk Distance
Left ventricular assist devices (LVAD) are increasingly becoming an accepted treatment option for medically refractory advanced heart failure patients who are non-transplant eligible. The prospective randomized clinical trial comparing the HeartMate II (HMII) and the HeartMate XVE LVADs demonstrated a significant improvement in survival and an overall reduction in adverse events for the HMII. Significant improvements in quality of life and functional status have also been reported during LVAD support. The results of the clinical trial led to the Food and Drug Administration (FDA) approval of the HMII as destination therapy (DT). The approval of HMII as both bridge-to-transplantation (BTT) in April 2008 and DT in January 2010 has now made mechanical circulatory support therapy available to a wider group of patients. Over 6000 patients have been supported by the HMII either as BTT or DT from 2004 through 2010, with nearly 3000 US patients receiving the device after FDA approval, whose data have already reported in the national INTERMACS registry.

However, new surgical advances do have a learning curve, and improvements in outcomes with increasing clinical experience should be expected. This has been previously evident in the HMII BTT experience where one year survival increased from 68% reported in the original cohort of patients enrolled from March 2005- May 2006 to 73% in the mid-trial update, to 85% in the post-approval study representing the first cohort of patients supported by this device in a commercial setting. Furthermore, recent publications from single center publications have reported similar outcomes in a diverse group of patients. For example, Adamson et al outlined clinical strategies and approaches that may help towards achieving good outcomes in elderly patients, where they reported a 2 year survival of 70% in patients older than 70 years receiving an LVAD.
Other studies have investigated HMII in restrictive and hypertrophic cardiomyopathies\(^9\), relationship between the acuity of heart failure with improved survival and length of stay\(^11\), as well as reversal of heart failure that can be achieved with an LVAD in combination with pharmacologic therapy\(^12\).

Patients in the original DT trial were enrolled at the same time as those in the initial BTT cohort, but had a longer follow up than the BTT patients. Since results of the first 133 HMII DT patients were published\(^2\), an additional 600 patients have been enrolled into the clinical trial as part of a continued access protocol (CAP). The goal of this report is to compare outcomes in patients enrolled later in the trial under CAP with outcomes of the initial primary patient cohort. The main hypothesis is that patients implanted in the later part of the trial would have better clinical outcomes compared to those who were implanted earlier.

**Methods**

This study is a retrospective analysis of patients enrolled in the multicenter HMII DT trial who were followed up for at least 2 years after HMII LVAD implantation. Only patients who received the HMII device for DT were included. Patients who received the HeartMate XVE in the randomized part of the trial or received a HMII as an exchange for a HeartMate XVE were excluded from the analysis. The clinical trial was supervised and monitored by Thoratec Corporation. A data and safety monitoring board (DSMB) consisting of 4 independent physicians and 1 biostatistician who were not investigators, met regularly to review study compliance, adverse events, quality of life, and outcomes. The study was conducted in compliance with FDA regulations for Good Clinical
Practices. The protocol was approved by the FDA and the institutional review board at each participating center. The academic authors vouch for the completeness and accuracy of the data.

**Study Subjects**

Details on the study inclusion and exclusion criteria for the DT trial are published elsewhere². Patients with advanced heart failure who were ineligible for heart transplantation, and were refractory to optimal medical management were considered for enrollment. Enrolled patients met the following criteria: ejection fraction of less than 25%, peak VO₂ < 14 ml/kg/min or less than 50% of the predicted value, New York Heart Association (NYHA) class IIIb or IV symptoms for at least 45 of the 60 days, or dependence on an intra-aortic balloon pump (IABP) for 7 days or inotropes for a period of at least 14 days before enrollment. Patients were excluded for severe renal (serum creatinine >3.5 mg/dL or long-term dialysis), hepatic (international normalized ratio [INR] > 2.5, total bilirubin > 5 mg/dL, or transaminases > 2000 U/L) or pulmonary (severe chronic obstructive pulmonary disease) dysfunction. Patients with uncontrolled infections, previous strokes, mechanical aortic valves, irreparable aortic insufficiency, aortic aneurysm >5.0 cm, or other mechanical circulatory support devices (except intra-aortic balloon pumps [IABPs]) also were excluded. Enrolled subjects with clinical follow up data for at least 2 years post implant were included in this sub-analysis.

Patients were divided into two groups: a) Early Trial group comprising the initial 133 patients implanted with a HMII who were enrolled from March 2005 – May 5, 2007 (ref 2); b) Mid Trial group comprising of 281 consecutive patients enrolled under the
continued access protocol from May 5, 2007 – March 31, 2009. All patients had a minimum clinical follow-up for at least 2 years since implant or until clinical outcome.

**Data Collection Baseline Assessment**

Data analyzed included patient characteristics and demographics (age, sex, heart failure etiology, NYHA class, history of prior stroke, body surface area (BSA), weight), baseline hemodynamics (left ventricular ejection fraction (LVEF), cardiac index (CI), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), pulmonary artery pressure, systemic blood pressure), laboratory values (creatinine, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, serum sodium), and baseline device/medical therapy (cardiac resynchronization therapy (CRT), implantable cardioverter-defibrillator (ICD), ventilator support, intra-aortic balloon pump (IABP), ace inhibitors, beta-blockers, and inotropes). In addition, the model for end-stage liver disease (MELD) and destination therapy risk score (DTRS)\textsuperscript{13} was calculated for each patient at implantation.

**Follow-up after Device Implantation**

Postoperative medical care (including inotropic, antiarrhythmic, anticoagulant and heart-failure therapy) was managed according to each investigator’s preference and usual practice. Device performance, laboratory results, and medication use were initially recorded at daily to weekly intervals until hospital discharge, and then were recorded monthly. All deaths of patients and causes of death were determined at autopsy when possible or by examination of medical records or by interviews with family members. Final adjudication was determined by the clinical events committee.
Outcomes

Kaplan-Meier survival was evaluated and compared for both the patient groups. Survival free from disabling stroke and reoperation to repair or replace the LVAD at 2 years was evaluated and was compared between the Early and Mid Trial patient groups using as-treated analysis. Other secondary outcomes comprised of functional capacity, quality of life, and adverse events. Functional assessments and quality of life (QoL) questionnaires were obtained at baseline when possible before LVAD implantation and at months 1, 3, 6, 12, 18, and 24 months. Functional status measurements included independently assessed NYHA functional class, and 6-minute walk distances (6MWD). Heart failure–related QoL was assessed using responses from the Minnesota Living with Heart Failure (MLWHF) and the Kansas City Cardiomyopathy questionnaires (KCCQ). Adverse events were recorded throughout the study until the analysis cutoff date with the use of standardized definitions (see the supplementary appendix of ref 2).

Statistical Analysis

Differences between groups of independent, normally distributed, continuous variables were evaluated using the t test. Variables that were not normally distributed were evaluated using the non-parametric Mann-Whitney U test. Differences in categorical variables were evaluated using the Fisher’s exact test or Pearson Chi-Squared test for more than 2 groups. Survival analysis was performed using the Kaplan-Meier method with patients censored for ongoing device support, transplantation, recovery of the native heart function with device removal, or withdrawal from the study. Comparison of survival between the two groups was performed using the log-rank test. Adverse events are presented as both percentages of patients and event rates (events per patient
year). Risk ratio evaluation and comparison of adverse event rates between the two groups were performed using Cochran-Mantel-Haenszel statistics. Adverse events in the Mid Trial group were compared to those reported by Slaughter et al. for the Early Trial group. Comparisons of quality of life over time were performed using repeated measures linear mixed effects modeling with a compound symmetry covariance structure. Model parameters included time, group (Early Trial/Mid Trial), and time*group. Time was modeled as a categorical variable with measurement time points of baseline, 1, 3, 6, 12, 18, and 24 months. Similarly, for comparing post-discharge INR values over time, a linear mixed effects model was used with the exception that only INR lab values at discharge or at post-discharge monthly intervals were retained for the analysis. All comparisons were two-sided with the level of significance set at p< 0.05. Statistical analyses were done using Systat (Cranes Software, Chicago, Ill) and SAS (SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics

Baseline parameters were characteristic of extremely ill patients with advanced heart failure. Patients in the Mid Trial group were similar for all parameters except for slightly smaller body surface area and weight (Table 1). Predicted 1-year survival rates, if patients had remained on medical management, were not significantly different between the groups, and were less than 50% for both groups using the Seattle Heart Failure Model.
Outcomes

Median duration of support was 1.7 years (range, 0.0 to 6) for the Early Trial group and 2.1 years (range, 0.0 to 4) for the Mid Trial group with a cumulative follow up duration of 280 and 498 patient-years respectively. Kaplan Meier survival (Figure 1) at 12 and 24 months for the Mid Trial group were 73 ± 3% and 63 ± 3% compared to the Early Trial experience of 68 ± 4% and 58 ± 4% (p=0.209 log-rank test). The percentage of patients reaching the endpoint of survival free from disabling stroke and reoperation to replace the device at 2 years in the Mid Trial group was 59% [166/281] compared to 50% in the Early Trial group [66/133] (p=0.073). There was trend of reduction in disabling stroke at 2 years at 6% [17/281] in the Mid Trial compared to 11%, [15/133] in the Early Trial (p=0.076). There was no difference between Mid Trial and Early Trial groups in the percentage of patients who were discharged from the hospital (87% [244/281] vs. 86% [114/133], p=0.760), although the median length of initial hospitalization was improved from 27 to 23 days (Early vs. Mid Trial) (p = 0.091).

Functional Assessment and Quality of Life

Early and sustained improvements in quality of life were seen in both groups, and there was a trend towards patients experiencing a better quality of life in the Mid Trial group compared to Early Trial (Figure 2). KCCQ overall summary score (OSS) were similar at baseline at 28 ± 18 (Mid Trial) and 27 ± 16 (Early Trial) and showed improvement in both groups by 6 months at 70 ± 21 in the Mid Trial group which was slightly greater than 64 ± 20 for the Early Trial group. There were sustained improvements in both groups for 24 months, with a trend for KCCQ scores to be higher in the Mid Trial group compared to the early trial group (p=0.080). MLWHF total score
showed similar improvements for both groups, with significantly better scores seen in the Mid Trial compared to Early Trial groups (p=0.043).

Significant improvements in functional status over time were observed in both the Early and Mid Trial groups (Figure 3). Over 80% of patients tested in both groups improved to NYHA Class I/II from NYHA Class IIIB/IV by 6 months, and was sustained through to 24 months. Six minute walk distance for patients who could walk at baseline was 181 ± 138 (ET, n=52) and 225 ± 142 meters (MT, n=98), which improved to over 340 m by 6 months and was sustained through 24 months in both groups.

Adverse Events

A comparison of adverse events between the two groups is shown in Table 2. There were statistically significant reductions in adverse events between the Early and Mid Trial groups in bleeding requiring transfusions (1.66 vs. 1.13 events / patient-year, RR=0.69, p<0.001), sepsis (0.38 vs. 0.27, RR=0.70, p=0.025), device related infections (0.47 vs. 0.27 events/patient-year, RR=0.56, p<0.001), cardiac arrhythmias (0.69 vs. 0.46, RR=0.67, p=0.003), and hemorrhagic stroke (0.07 vs. 0.03 events/patient-year, RR=0.40, p=0.012). The rates of other adverse events including ischemic stroke, pump thrombosis, and pump replacements were similar between the two groups.

Causes of Death

Primary causes of death within the first 2 years of support are shown in Table 3. Hemorrhagic stroke was the most common cause of death in the Early Trial group (8% [10/133]), which was significantly reduced to 2% (6/281) in the Mid Trial group (p=0.012). Deaths due to hemorrhagic stroke tended to occur sooner in the Early Trial group (231 ± 180 days) compared to the Mid Trial group (351 ± 225 days) although the
difference was not statistically significant (p=0.193). In the first 6 months of support, 5 patients (3.8%) died of hemorrhagic stroke in the Early Trial, which was significantly reduced to 1 patient (0.3%) in the Mid Trial (p=0.014). However, there was no difference in the temporal occurrence of hemorrhagic stroke adverse events themselves (509 ± 419 days [Early Trial] vs. 469 ± 468 days [Mid Trial], p=0.810). There were no differences in other causes of death between the two groups including right heart failure (4% vs. 4%, p=1.00), bleeding (3% vs. 4%, p=1.00], sepsis (4% vs. 3%, p=0.764), ischemic stroke (1% vs. 3%, p=0.178), or multi-system organ failure (2% vs. 2%, p=1.00) for Early Trial vs. Mid Trial groups respectively.

**Anticoagulation Management**

Figure 4 shows the proportion of patients receiving heparin in the immediate postoperative period in transition to long term warfarin therapy. There were significant differences between the two groups in the proportion of patients receiving therapeutic, sub-therapeutic, and no heparin post-op as a transition to Warfarin therapy (p=0.004). A larger proportion of patients did not receive heparin in the Mid Trial group (38%) compared to the Early Trial group (22%). Figure 5 shows the post-discharge INR values and the variability over time for both the Early and Mid-trial groups. The median post discharge INR for all follow up time points was lower in the Mid Trial group (1.8 [25th – 75th percentile: 1.4 – 2.3]) compared to the Early Trial group (1.9 [25th-75th percentile: 1.4-2.4 , p=0.028]). In addition, there was a smaller proportion of INR measurements greater than 2.5 in the Mid-Trial group (18%) compared to the Early-Trial group (21%). The largest change in INR values was at hospital discharge, where median INR dropped from 2.3 at discharge in the Early Trial to 1.9 in the Mid Trial, and the percentage of INR
values above 2.5 decreased from 29% to 17%. By six months of support, the percentage of INR values above 2.5 had dropped slightly in the early trial group to 27%, but was still higher than in the mid trial group (19%).

Discussion

This study demonstrates that outcomes in advanced heart failure patients treated with a continuous flow left ventricular assist device (HeartMate II) as destination therapy have continued to improve during the course of the clinical trial. Importantly, there were statistically significant reductions in serious adverse events including the incidence of hemorrhagic strokes, bleeding, driveline infection, and sepsis. Survival rates are now 73% at 1 year and 63% at 2 years. The 50% reduction in the incidence of hemorrhagic strokes directly had an impact on mortality, with hemorrhagic strokes being the cause of death in only 2% of mid trial patients as opposed to 8% in the early part of the trial.

Improvements in outcomes are expected with increasing clinical experience with any new surgical therapy. However, in the case of the pulsatile HeartMate XVE LVAS, there was no improvement in survival between the original REMATCH study and the most recent randomized DT trial (One year survival: 52% vs. 55%), due to the limited durability of the device. Conversely, there has been a consistent improvement in outcomes in the HeartMate II BTT experience with an increase in 1 year survival from 68% to 73% during the trial, and 85% in the post trial experience. Some of these improvements observed can be attributed to better patient selection for the therapy, while others are possibly due to improved patient management pre and post LVAD implant. These observations have resulted in an update of management guidelines for the HMII.
In the current study, most improvements are probably due to better post-operative and post-discharge patient management since the characteristics of patients selected were similar between the two cohorts, and the survival rates were similar for the first 60 days before showing a trend for improvement.

Reduction in hemorrhagic strokes and bleeding events could partly be attributed to improved anticoagulation regimen tailored specifically to the HMII. Initial recommendation for the HM II involved heparin in the immediate post-operative period, followed by warfarin with a target INR of 2.0 – 3.0, aspirin (81 to 100 mg daily), and dipyridamole. Target INR range for warfarin therapy has now been reduced to 1.5 – 2.5 based on recent clinical findings reported by Boyle et al 17. Additionally, patients with a HMII have been reported to have increased bleeding due to acquired von Willebrand syndrome, which reduces platelet binding and activity 18, 19. Also, recent clinical experiences have shown that heparin may not be needed in transition to warfarin in the post-operative period 20. Slaughter et al demonstrated that there was no difference in thrombotic events between patients who were transitioned to warfarin on heparin and those who were not. Furthermore, patients who were not on heparin experienced lesser number of bleeding events 20.

Changes in recommendations of anticoagulation management have been highlighted in the updated patient management guidelines for HMII 16. Results in the current study also indicate a general trend as the trial progressed of less use of heparin for bridging to warfarin along with a lower target INR, a trend which was most evident in the first 6 months of the early part of the trial (Figures 4 and 5). With respect to anti-platelet medications, there were not enough data in the trial to make any conclusions on their
impact on bleeding and hemorrhagic strokes. Changes to the anticoagulation strategy could be one of the contributing factors leading to an overall reduction in bleeding and hemorrhagic stroke events in the Mid Trial group.

Introduction of the HMII and smaller sized continuous flow LVADs have significantly reduced the incidence of driveline infections and sepsis from the pulsatile LVADs\(^2\). However, infection continues to be a significant source of morbidity and one of the primary reasons for prolonged hospital length of stay\(^2\)\(^1\) and hospital readmissions. As more patients are on mechanical circulatory support for longer periods of time, there is an increasing need for reducing driveline infections. Our study has shown an additional reduction in driveline infection, localized non-device related infection, and sepsis event rates in the mid trial period. The finding indicates that both clinicians and patients have learned from the early trial experience, and were more cognizant about the importance of stabilization of the driveline, management of the driveline exit site, and overall patient management which eventually resulted in lower infection rates.

From the results of this updated study in 281 destination therapy patients, we can infer a magnitude of the survival benefit of continuous flow LVAD compared to the medical arm of REMATCH representing optimal medical management for 2001, which is shown in Figure 6.

**Conclusions**

The benefit of DT therapy with the HM II is confirmed in subsequent trial patients. The survival rates in these patients are now 73% at 1 year and 63% at 2 years. These were substantial reductions in serious adverse events including hemorrhagic strokes (>...
50% reduction), localized non device related infection (35% reduction), sepsis (30%
reduction), device related infections (>40% reduction), bleeding requiring transfusion
(>30% reductions) and cardiac arrhythmias (> 30% reduction). There were also fewer
deaths due to hemorrhagic strokes. These improvements highlight that both clinicians and
patients are benefiting from the increasing clinical experience associated with the use of
HeartMate II for long term treatment of advanced heart failure, which are directly getting
translated to improving clinical outcomes.
<table>
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<tr>
<th>Author</th>
<th>Disclosure</th>
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<tbody>
<tr>
<td>Soon J. Park, MD</td>
<td>Research and Training Grant from Thoratec Corp</td>
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<tr>
<td>Joseph G. Rogers, MD</td>
<td>Consultant, Thoratec Corporation</td>
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<td>Training and Occasional Speaking for Thoratec Corp</td>
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<td>Consulting Fee, Modest &lt; $10,000</td>
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<tr>
<td>Kartik S. Sundareswaran, PhD</td>
<td>Employee of Thoratec Corp</td>
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<tr>
<td>David J. Farrar, PhD</td>
<td>Employee of Thoratec Corp</td>
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<tr>
<td>Mark S. Slaughter, MD</td>
<td>Research Support from Thoratec Corp</td>
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References


Table 1. Comparison of baseline characteristics of patients in the Early Trial and Mid Trial groups

<table>
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<tr>
<th>Characteristic</th>
<th>Early Trial</th>
<th>Mid Trial</th>
<th>P value</th>
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<tr>
<td>Patients Enrolled</td>
<td>133</td>
<td>281</td>
<td>-</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>62.5 ± 11.5</td>
<td>63.3 ± 12.6</td>
<td>0.282</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>107 (80%)</td>
<td>221 (79%)</td>
<td>0.699</td>
</tr>
<tr>
<td>Ischemic Etiology (%)</td>
<td>88 (66%)</td>
<td>163 (58%)</td>
<td>0.132</td>
</tr>
<tr>
<td>NYHA Class IV (%)</td>
<td>95 (71%)</td>
<td>178 (63%)</td>
<td>0.120</td>
</tr>
<tr>
<td>History of Prior Stroke (%)</td>
<td>22 (17%)</td>
<td>39 (14%)</td>
<td>0.765</td>
</tr>
<tr>
<td>Body Surface Area (m²)</td>
<td>2.03 ± 0.26</td>
<td>1.96 ± 0.26</td>
<td>0.018</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86 ± 20</td>
<td>81 ± 19</td>
<td>0.011</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>17 ± 6</td>
<td>17 ± 6</td>
<td>0.387</td>
</tr>
<tr>
<td>Cardiac Index (L/min/m²)</td>
<td>2.06 ± 0.57</td>
<td>2.03 ± 0.62</td>
<td>0.567</td>
</tr>
<tr>
<td>Central Venous pressure (mmHg)</td>
<td>12.8 ± 6.2</td>
<td>13.0 ± 6.6</td>
<td>0.776</td>
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<td>Pulmonary Capillary Wedge Pressure (mmHg)</td>
<td>24.1 ± 8.4</td>
<td>24.4 ± 7.9</td>
<td>0.699</td>
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<tr>
<td>Pulmonary Vascular Resistance (W.U.)</td>
<td>3.29 ± 1.63</td>
<td>3.57 ± 1.83</td>
<td>0.273</td>
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<td>Systolic Blood Pressure (mmHg)</td>
<td>103 ± 15</td>
<td>103 ± 15</td>
<td>0.492</td>
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<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>60 ± 13</td>
<td>63 ± 12</td>
<td>0.080</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>1.59 ± 0.58</td>
<td>1.53 ± 0.58</td>
<td>0.214</td>
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<td>Blood Urea Nitrogen (mg/dl)</td>
<td>37.7 ± 25.3</td>
<td>34.2 ± 18.8</td>
<td>0.589</td>
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<tr>
<td>Alanine Aminotransferase (U/L)</td>
<td>39 ± 37</td>
<td>42 ± 66</td>
<td>0.343</td>
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<tr>
<td>Aspartate Aminotransferase (U/L)</td>
<td>36 ± 47</td>
<td>40 ± 62</td>
<td>0.132</td>
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<tr>
<td>Metric</td>
<td>Control Group Mean ± SD</td>
<td>Intervention Group Mean ± SD</td>
<td>p-value</td>
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<tr>
<td>---------------------------------------------</td>
<td>-------------------------</td>
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<tr>
<td>Total Bilirubin (mg/dl)</td>
<td>1.21 ± 0.76</td>
<td>1.21 ± 0.86</td>
<td>0.957</td>
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<td>Serum Sodium (mmol/L)</td>
<td>134.8 ± 4.3</td>
<td>135.0 ± 4.5</td>
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<td>Biventricular Pacemaker (%)</td>
<td>85 (64%)</td>
<td>166 (59%)</td>
<td>0.389</td>
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<td>Implantable Cardioverter – Defibrillator (%)</td>
<td>109 (82%)</td>
<td>233 (83%)</td>
<td>0.890</td>
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<td>Ventilator Support (%)</td>
<td>9 (7%)</td>
<td>10 (4%)</td>
<td>0.206</td>
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<td>Intra-Aortic Balloon pump (%)</td>
<td>30 (23%)</td>
<td>53 (19%)</td>
<td>0.430</td>
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<tr>
<td>Ace Inhibitors (%)</td>
<td>44 (33%)</td>
<td>79 (28%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>72 (54%)</td>
<td>134 (48%)</td>
<td>0.247</td>
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<tr>
<td>Inotropes (%)</td>
<td>102 (77%)</td>
<td>220 (78%)</td>
<td>0.706</td>
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<tr>
<td>MELD</td>
<td>14.0 ± 4.5</td>
<td>13.7 ± 4.8</td>
<td>0.455</td>
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<tr>
<td>DTRS</td>
<td>10.8 ± 5.3</td>
<td>10.3 ± 5.6</td>
<td>0.531</td>
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<tr>
<td>Estimated 1-year survival with SHFM</td>
<td>38.4 ± 28.4%</td>
<td>42.3 ± 29.4%</td>
<td>0.279</td>
</tr>
</tbody>
</table>

SD – standard deviation, RVSWI – right ventricular stroke work index, NYHA – New York Heart Association, AST – serum aspartate aminotransaminase, ALT – serum alanine aminotransaminase, LDH – lactate dehydrogenase, ACE - angiotensin converting enzyme, ICD - implantable cardioverter defibrillator, IABP - intra-aortic balloon pump, MELD= Model for End Stage Liver Disease , DTRS =Destination Therapy Risk Score , SHFM = Seattle Heart Failure Model
Table 2. Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Early Trial (N=133; 211 Patient Years)</th>
<th>Mid Trial (N=281; 498.0 Patient Years)</th>
<th>Risk Ratios</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (%)</td>
<td>Events (Event Rate)</td>
<td>Patients (%)</td>
<td>Events (Event Rate)</td>
</tr>
<tr>
<td><strong>Bleeding requiring PRBC</strong></td>
<td>108 (81%) 349 (1.66)</td>
<td>207 (74%) 565 (1.13)</td>
<td>0.69 [0.56-0.84]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Bleeding: requiring re-exploration</strong></td>
<td>40 (30%) 49 (0.23)</td>
<td>55 (20%) 68 (0.14)</td>
<td>0.72 [0.47-1.10]</td>
<td>0.126</td>
</tr>
<tr>
<td><strong>Infection:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local non-device related</strong></td>
<td>65 (49%) 160 (0.76)</td>
<td>126 (45%) 244 (0.49)</td>
<td>0.65 [0.50 - 0.83]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td>48 (41%) 81 (0.38)</td>
<td>78 (28%) 133 (0.27)</td>
<td>0.70 [0.50 - 0.96]</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Device-related</strong></td>
<td>47 (35%) 100 (0.47)</td>
<td>84 (30%) 133 (0.27)</td>
<td>0.56 [0.41 - 0.76]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Driveline Infection</strong></td>
<td>42 (32%) 80 (0.38)</td>
<td>75 (27%) 110 (0.22)</td>
<td>0.58 [0.42 - 0.81]</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Pocket Infection</strong></td>
<td>12 (9%) 19 (0.09)</td>
<td>20 (7%) 23 (0.05)</td>
<td>0.51 [0.27 - 0.96]</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>Cardiac arrhythmias: cardioversion / defibrillation</strong></td>
<td>75 (56%) 145 (0.69)</td>
<td>141 (50%) 229 (0.46)</td>
<td>0.67 [0.51 - 0.87]</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
<td>21 (16%) 21 (0.10)</td>
<td>30 (11%) 31 (0.06)</td>
<td>0.62 [0.35-1.11]</td>
<td>0.108</td>
</tr>
<tr>
<td><strong>Right heart failure</strong></td>
<td>31 (23%) 34 (0.16)</td>
<td>58 (21%) 66 (0.13)</td>
<td>0.82 [0.53 - 1.28]</td>
<td>0.386</td>
</tr>
<tr>
<td><strong>RVAD</strong></td>
<td>5 (4%) 5 (0.02)</td>
<td>17 (6%) 7 (0.03)</td>
<td>1.44 [0.52 - 3.95]</td>
<td>0.478</td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td>11 (8%) 12 (0.06)</td>
<td>22 (8%) 23 (0.05)</td>
<td>0.81 [0.40 - 1.66]</td>
<td>0.567</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>15 (11%) 15 (0.07)</td>
<td>13 (5%) 14 (0.03)</td>
<td>0.40 [0.19 - 0.83]</td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td><strong>Other neurological events (eg, TIA, seizures, confusion, etc)</strong></td>
<td>29 (22%) 35 (0.17)</td>
<td>49 (17%) 58 (0.12)</td>
<td>0.70 [0.45 - 1.10]</td>
<td>0.121</td>
</tr>
<tr>
<td><strong>Hemolysis</strong></td>
<td>5 (4%) 5 (0.02)</td>
<td>13 (5%) 14 (0.03)</td>
<td>1.19 [0.42 - 3.33]</td>
<td>0.747</td>
</tr>
<tr>
<td><strong>Pump Replacement</strong></td>
<td>12 (9%) 13 (0.06)</td>
<td>22 (8%) 22 (0.04)</td>
<td>0.72 [0.35 - 1.45]</td>
<td>0.352</td>
</tr>
<tr>
<td><strong>Pump Replacement – Thrombus</strong></td>
<td>2 (2%) 2 (0.01)</td>
<td>8 (3%) 8 (0.02)</td>
<td>1.69 [0.36 - 8.04]</td>
<td>0.503</td>
</tr>
<tr>
<td><strong>Pump Thrombosis</strong></td>
<td>5 (4%) 5 (0.024)</td>
<td>16 (6%) 19 (0.038)</td>
<td>1.61 [0.59 - 4.36]</td>
<td>0.347</td>
</tr>
</tbody>
</table>

* Includes extended inotropic support

Adverse events for the Early Trial group are as reported by Slaughter et al².
Table 3. Primary Causes of Death at 2 Years. Other causes of death include air embolism, anoxic brain injury, traumatic brain injury, cardiac arrest, cardiac failure, heart failure, respiratory failure, pneumonia, amyloidosis, cancer, liver failure, pancreatitis, withdrawal of support, respiratory failure, ruptured bladder, subdural hematoma, and unknown.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Early Trial</th>
<th>Mid trial</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic stroke</td>
<td>10 (8%)</td>
<td>6 (2%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>5 (4%)</td>
<td>12 (4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4 (3%)</td>
<td>10 (4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (4%)</td>
<td>8 (3%)</td>
<td>0.764</td>
</tr>
<tr>
<td>MOF</td>
<td>2 (2%)</td>
<td>5 (2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1 (1%)</td>
<td>9 (3%)</td>
<td>0.178</td>
</tr>
<tr>
<td>External components / Loss of Power</td>
<td>4 (3%)</td>
<td>5 (2%)</td>
<td>0.477</td>
</tr>
<tr>
<td>Internal components (6 thrombosis; 2 cable)</td>
<td>3 (2%)</td>
<td>7 (2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Other</td>
<td>18 (14%)</td>
<td>36 (13%)</td>
<td>0.876</td>
</tr>
</tbody>
</table>
Figure Legends

**Figure 1.** Comparison of Kaplan-Meier Survival between the Early and Mid Trial groups.

**Figure 2.** Comparison of Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (left) and the Minnesota Living with Heart Failure Questionnaire (MLWHF) total score (right) between the Early and Mid Trial Groups.

**Figure 3.** Comparison of: six minute walk distance (6MWD, left); and percent of ongoing patients with New York Heart Association (NYHA) functional class improvement to class I or II (right) between the Early and Mid Trial groups.

**Figure 4.** Proportion of patients bridged with Heparin in the Early and Mid Trial Groups. There were fewer patients transitioned to Warfarin using Therapeutic Heparin, or Sub-Therapeutic Heparin, and more patients with No Heparin in the Mid Trial group. Heparin groupings were determined using partial thromboplastin time as described by Slaughter and colleagues.

**Figure 5.** Box and whisker plots demonstrating INR values over time from discharge to 24 months post-implant.

**Figure 6.** Inference of the survival benefit of current destination therapy with current continuous flow LVAD compared to medical management from the REMATCH trial.
Figure 1

Average Support Duration

Early Trial = 2.1 ± 1.8 years (Longest: 6 years)
Mid Trial = 1.8 ± 1.2 years (Longest: 4 years)

At Risk

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Early Trial (N=133)</th>
<th>Mid-Trial (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>281</td>
<td>73 ± 3%</td>
</tr>
<tr>
<td>6</td>
<td>215</td>
<td>68 ± 4%</td>
</tr>
<tr>
<td>12</td>
<td>187</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>165</td>
<td>63 ± 3%</td>
</tr>
<tr>
<td>24</td>
<td>146</td>
<td>58 ± 4%</td>
</tr>
</tbody>
</table>

P (Log-Rank)=0.209
Figure 2

KCCQ

Overall Summary Score

Mid Trial (N=281)
Early Trial (N=133)

Pts Tested
115 89 86 76 62 56
245 201 187 161 133 114

P < 0.001 over time
P = 0.080 between groups
P = 0.308 interaction

MLWHF

Total Score

Mid Trial (N=281)
Early Trial (N=133)

Pts Tested
116 89 86 75 62 53
250 195 184 155 126 108

P < 0.001 over time
P = 0.043 between groups
P = 0.416 interaction
Figure 3

6MWD

P < 0.001 over time
P = 0.907 between groups
P = 0.044 interaction

NYHA Class I or II

<table>
<thead>
<tr>
<th>Months</th>
<th>Baseline</th>
<th>6 Mo</th>
<th>12 Mo</th>
<th>18 Mo</th>
<th>24 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts Tested</td>
<td>125</td>
<td>85</td>
<td>73</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>267</td>
<td>191</td>
<td>161</td>
<td>130</td>
<td>103</td>
</tr>
</tbody>
</table>

Mid Trial (N=281)
Early Trial (N=133)
Figure 5

INR

Early Trial
Mid Trial

Discharge 6 Months 12 Months 18 Months 24 Months

P=0.001 (between groups)
Figure 6

- LVAD Destination Therapy (HMII Trial)
  - 73% survival at 2 years
  - 63% survival at 4 years

- Medical Management (REMATCH, NEJM 2001)
  - 27% survival at 2 years
  - 8% survival at 4 years

Survival (%) vs. Months
Outcomes in Advanced Heart Failure Patients with Left Ventricular Assist Devices for Destination Therapy

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