

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

Soon J. Park, MD; Carmelo A. Milano, MD; Antone J. Tatroles, MD; Joseph G. Rogers, MD; Robert M. Adamson, MD; D. Eric Steidley, MD; Gregory A. Ewald, MD; Kartik S. Sundareswaran, PhD; David J. Farrar, PhD; Mark S. Slaughter, MD; for the HeartMate II Clinical Investigators†

**Background**—The HeartMate II (HMII) destination therapy (DT) trial demonstrated significant improvements in outcomes in continuous-flow left ventricular assist devices compared with 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 to March 2009 (Mid Trial [MT] group) were compared with the initial 133 HMII patients from March 2005 to May 2007 (Early Trial [ET] group). Patient entry criteria were the same during the 2 time periods. Survival, adverse events, and quality of life were compared between the 2 groups. Baseline characteristics were similar between the groups. Compared with the ET group, patients in the MT group had reduced adverse event rates for bleeding requiring transfusions (1.66 versus 1.13 events per patient-year,  $P<0.001$ ), sepsis (0.38 versus 0.27,  $P=0.025$ ), device-related infections (0.47 versus 0.27,  $P<0.001$ ), and hemorrhagic stroke (0.07 versus 0.03,  $P=0.01$ ). Other event rates were similar between groups including ischemic stroke (0.06 versus 0.05 events per patient-year,  $P=0.57$ ). Survival at 1 year in the MT group was 73% versus 68% in the ET group ( $P=0.21$ ). Additionally, there was a significant reduction in deaths caused by hemorrhagic stroke ( $P=0.01$ ). Quality of life improvements were significant in both the groups ( $P<0.001$ ).

**Conclusions**—The benefit of DT therapy with the HMII 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. (*Circ Heart Fail.* 2012;5:241-248.)

**Key Words:** heart failure ■ mechanical circulatory support ■ ventricular assist device ■ HeartMate II

Left ventricular assist devices (LVAD) are increasingly becoming an accepted treatment option for medically refractory advanced heart failure patients who are non-transplant eligible.<sup>1-3</sup> 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.<sup>2,3</sup> Significant improvements in quality of life and functional status have also been reported during LVAD support.<sup>4</sup> 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. More than 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.<sup>5</sup>

## Clinical Perspective on p 248

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, in which 1-year survival increased from 68% reported in the original cohort of patients enrolled from March 2005 to May 2006<sup>6</sup> to 73% in the midtrial update,<sup>7</sup> to 85% in the postapproval study representing the first cohort of patients supported by this device in a commercial setting.<sup>8</sup> Furthermore, recent publications from single center publications have reported similar outcomes in a diverse group of patients.<sup>9-12</sup> For example,

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From the Mayo Clinic, Rochester, MN (S.J.P.), and Phoenix, AZ (D.E.S.); Duke University, Durham, NC (C.A.M., J.G.R.); Advocate Christ Medical Center, Chicago, IL (A.J.T.); Sharp Memorial Hospital, San Diego, CA (R.M.A.); Washington University, St Louis, MO (G.A.E.); Jewish Hospital, Louisville, KY (M.S.S.); and Thoratec, Pleasanton, CA (K.S.S., D.J.F.).

†A complete list of study investigators has been previously published (*N Engl J Med.* 2009;361:2241-2251).

Correspondence to Soon J. Park, MD, Division of Cardiac Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail [park.soon@mayo.edu](mailto:park.soon@mayo.edu)  
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Adamson et al<sup>10</sup> outlined clinical strategies and approaches that may help toward achieving good outcomes in elderly patients, in which 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,<sup>9</sup> relationship between the acuity of heart failure with improved survival and length of stay,<sup>11</sup> as well as reversal of heart failure that can be achieved with an LVAD in combination with pharmacological therapy.<sup>12</sup>

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,<sup>2</sup> an additional 600 patients have been enrolled into the clinical trial as part of a continued access protocol. The goal of this report is to compare outcomes in patients enrolled later in the trial under continued access protocol 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 with 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, 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 elsewhere.<sup>2</sup> 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 <25%, peak  $\text{VO}_2$  <14 mL/kg per minute or <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 IABPs) also were excluded. Enrolled subjects with clinical follow-up data for at least 2 years after implant were included in this subanalysis.

Patients were divided into 2 groups: (1) the Early Trial group, comprising the initial 133 patients implanted with a HMII who were enrolled from March 2005 to May 5, 2007,<sup>2</sup> and (2) the Mid Trial group, comprising 281 consecutive patients enrolled under the continued access protocol from May 5, 2007, to 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, weight), baseline hemodynamics (left ventricular ejection fraction, cardiac index, central venous pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, pulmonary artery pressure, and systemic blood pressure), laboratory values (creatinine, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and serum sodium), and baseline device/medical therapy (cardiac resynchronization therapy, implantable cardioverter-defibrillator, ventilator support, IABP, angiotensin-converting enzyme inhibitors,  $\beta$ -blockers, and inotropes). In addition, the model for end-stage liver disease (MELD) and destination therapy risk score (DTRS)<sup>13</sup> were 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 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. Heart failure–related quality of life was assessed by 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 Slaughter et al<sup>2</sup>).

## 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 nonparametric Mann-Whitney *U* test. Differences in categorical variables were evaluated using the Fisher exact test or Pearson  $\chi^2$  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 2 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 2 groups were performed using Cochran-Mantel-Haenszel statistics. Adverse events in the Mid Trial group were compared with those reported by Slaughter et al<sup>2</sup> 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 $\times$ 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 postdischarge INR values over time, a linear mixed-effects model was used with the exception that only INR laboratory values at discharge or at postdischarge monthly intervals were retained for the

**Table 1. Comparison of Baseline Characteristics of Patients in the Early Trial and Mid Trial Groups**

Characteristic	Early Trial	Mid Trial	P Value
Patients enrolled, n	133	281	...
Age, y	62.5±11.5	63.3±12.6	0.282
Male sex, %	107 (80%)	221 (79%)	0.699
Ischemic etiology, %	88 (66%)	163 (58%)	0.132
NYHA class IV, %	95 (71%)	178 (63%)	0.120
History of prior stroke, %	22 (17%)	39 (14%)	0.765
Body surface area, m <sup>2</sup>	2.03±0.26	1.96±0.26	0.018
Weight, kg	86±20	81±19	0.011
Left ventricular ejection fraction, %	17±6	17±6	0.387
Cardiac index, L/min per m <sup>2</sup>	2.06±0.57	2.03±0.62	0.567
Central venous pressure, mm Hg	12.8±6.2	13.0±6.6	0.776
Pulmonary capillary wedge pressure, mm Hg	24.1±8.4	24.4±7.9	0.699
Pulmonary vascular resistance, Wood U	3.29±1.63	3.57±1.83	0.273
Systolic blood pressure, mm Hg	103±15	103±15	0.492
Diastolic blood pressure, mm Hg	60±13	63±12	0.080
Creatinine, mg/dL	1.59±0.58	1.53±0.58	0.214
Blood urea nitrogen, mg/dL	37.7±25.3	34.2±18.8	0.589
Alanine aminotransferase, U/L	39±37	42±66	0.343
Aspartate aminotransferase, U/L	36±47	40±62	0.132
Total bilirubin, mg/dL	1.21±0.76	1.21±0.86	0.957
Serum sodium, mmol/L	134.8±4.3	135.0±4.5	0.510
Biventricular pacemaker, %	85 (64%)	166 (59%)	0.389
Implantable cardioverter-defibrillator, %	109 (82%)	233 (83%)	0.890
Ventilator support, %	9 (7%)	10 (4%)	0.206
Intra-aortic balloon pump, %	30 (23%)	53 (19%)	0.430
ACE inhibitors, %	44 (33%)	79 (28%)	0.303
β-blockers, %	72 (54%)	134 (48%)	0.247
Inotropes, %	102 (77%)	220 (78%)	0.706
MELD	14.0±4.5	13.7±4.8	0.455
DTRS	10.8±5.3	10.3±5.6	0.531
Estimated 1-y survival with SHFM	38.4±28.4%	42.3±29.4%	0.279

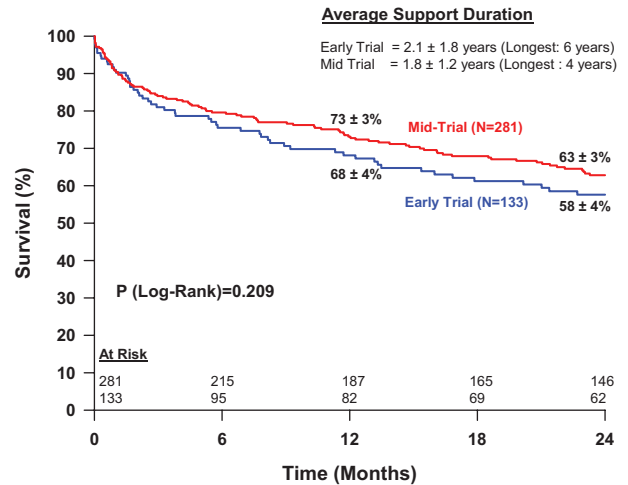
NYHA indicates New York Heart Association; ACE, angiotensin-converting enzyme; MELD, Model for End-Stage Liver Disease; DTRS, Destination Therapy Risk Score; SHFM, Seattle Heart Failure Model.

analysis. All comparisons were 2-sided, with the level of significance set at  $P < 0.05$ . Statistical analyses were done using Systat (Cranes Software, Chicago, IL) 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



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

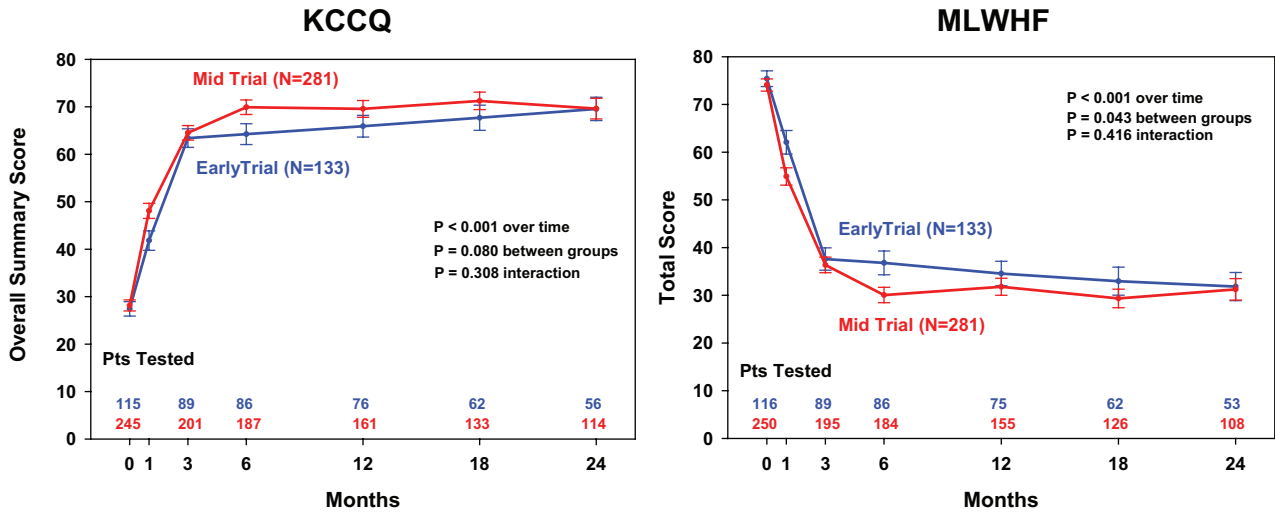
treatment, were not significantly different between the groups and were  $< 50\%$  for both groups using the Seattle Heart Failure Model.<sup>14</sup>

### Outcomes

Median duration of support was 1.7 years (range, 0.0–6) for the Mid Trial group and 2.1 years (range, 0.0–4) for the Early Trial group, with a cumulative follow-up duration of 280 and 498 patient-years, respectively. Kaplan-Meier survival curves (Figure 1) at 12 and 24 months for the Mid Trial group were  $73 \pm 3\%$  and  $63 \pm 3\%$ , compared with the Early Trial experience of  $68 \pm 4\%$  and  $58 \pm 4\%$  ( $P = 0.209$  log-rank test). The percentage of patients reaching the end point 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 with 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 with 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] versus 86% [114/133],  $P = 0.760$ ), although the median length of initial hospitalization was improved from 27 to 23 days (Early versus 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 toward patients having a better quality of life in the Mid Trial group compared with Early Trial (Figure 2). KCCQ overall summary score were similar at baseline at  $28 \pm 18$  (Mid Trial) and  $27 \pm 16$  (Early Trial) and showed improvement in both groups by 6 months at  $70 \pm 21$  in the Mid Trial group, which was slightly greater than  $64 \pm 20$  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 with 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 with Early Trial groups ( $P = 0.043$ ).



**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.

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

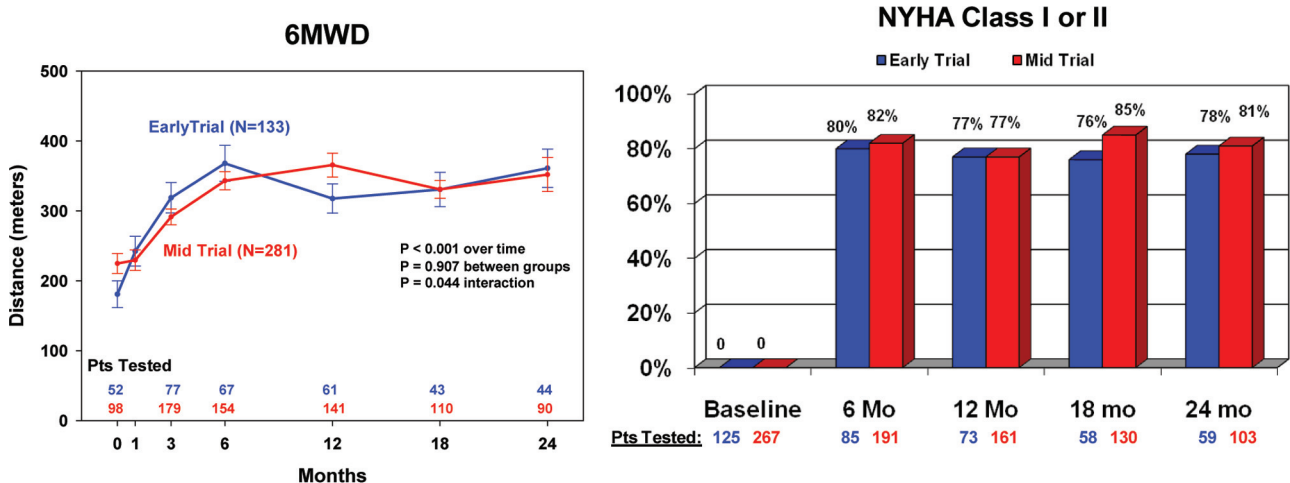
**Adverse Events**

A comparison of adverse events between the 2 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 versus 1.13 events per patient-year; risk ratio [RR]=0.69,  $P<0.001$ ), sepsis (0.38 versus 0.27,  $RR=0.70$ ,  $P=0.025$ ), device related infections (0.47 versus 0.27 events per patient-year,  $RR=0.56$ ,  $P<0.001$ ), cardiac arrhythmias (0.69 versus 0.46,  $RR=0.67$ ,  $P=0.003$ ), and hemorrhagic stroke (0.07 versus

0.03 events per 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 2 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 caused by hemorrhagic stroke tended to occur sooner in the Early Trial group ( $231 \pm 180$  days) compared with the Mid Trial group ( $351 \pm 225$  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 ( $509 \pm 419$  days [Early Trial] versus  $469 \pm 468$  days [Mid



**Figure 3.** Comparison of 6-minute walk distance (6MWD, left) and percentage 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.

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**Table 2. Adverse Events**

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

Adverse events for the Early Trial group are as reported by Slaughter et al.<sup>2</sup>

PRBC indicates packed red blood cells; RVAD, right ventricular assist device; TIA, transient ischemic attack.

\*Includes extended inotropic support.

Trial],  $P=0.810$ ). There were no differences in other causes of death between the 2 groups including right heart failure (4% versus 4%,  $P=1.00$ ), bleeding (3% versus 4%,  $P=1.00$ ), sepsis (4% versus 3%,  $P=0.764$ ), ischemic stroke (1% versus 3%,  $P=0.178$ ), or multisystem organ failure (2% versus 2%,  $P=1.00$ ) for Early Trial versus Mid Trial groups, respectively.

**Table 3. Primary Causes of Death at 2 Years**

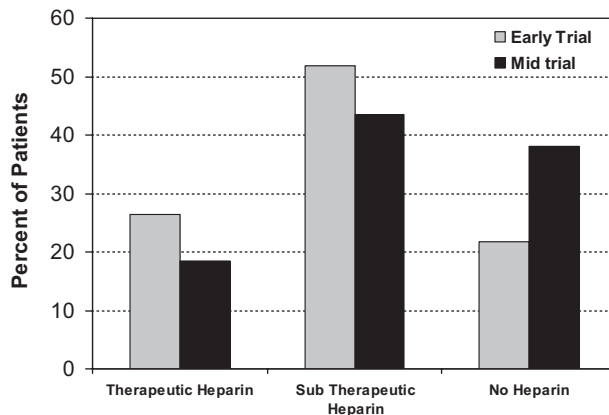
Cause	Early Trial	Mid Trial	P Value
Hemorrhagic stroke	10 (8%)	6 (2%)	0.012
Right heart failure	5 (4%)	12 (4%)	1.000
Bleeding	4 (3%)	10 (4%)	1.000
Sepsis	5 (4%)	8 (3%)	0.764
MOF	2 (2%)	5 (2%)	1.000
Ischemic stroke	1 (1%)	9 (3%)	0.178
External components/ loss of power	4 (3%)	5 (2%)	0.477
Internal components, 6 thrombosis; 2 cable	3 (2%)	7 (2%)	1.000
Other	18 (14%)	36 (13%)	0.876

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.

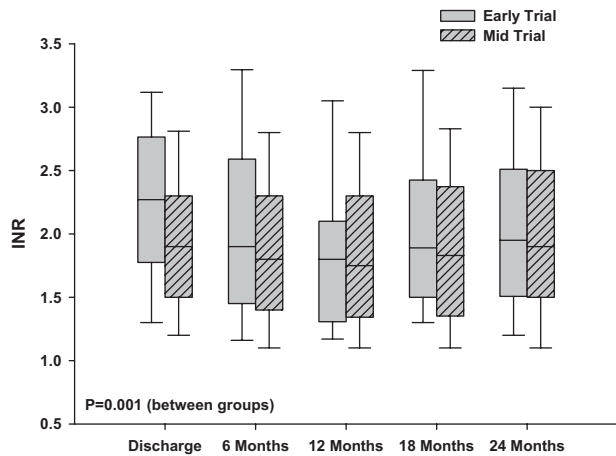
MOF indicates multiple organ failure.

**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 2 groups in the proportion of patients receiving therapeutic, subtherapeutic, and no heparin postoperatively as a transition to warfarin therapy ( $P=0.004$ ). A larger proportion of patients did not receive heparin in the Mid Trial group



**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 subtherapeutic heparin and more patients with no heparin in the Mid Trial group. Heparin groupings were determined using partial thromboplastin time as described by Slaughter et al.<sup>20</sup>



**Figure 5.** Box-and-whisker plots demonstrating international normalized ratio (INR) values over time from discharge to 24 months after implant.

(38%) compared with the Early Trial group (22%). Figure 5 shows the postdischarge INR values and the variability over time for both the Early and Midtrial groups. The median postdischarge INR for all follow-up time points was lower in the Mid Trial group (1.8 [25<sup>th</sup> to 75<sup>th</sup> percentile: 1.4–2.3]) compared with the Early Trial group (1.9 [25<sup>th</sup> to 75<sup>th</sup> percentile: 1.4–2.4,  $P=0.028$ ]). In addition, there was a smaller proportion of INR measurements  $>2.5$  in the Mid-Trial group (18%) compared with the Early-Trial group (21%). The largest change in INR values was at hospital discharge, in which 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  $>2.5$  decreased from 29–17%. By 6 months of support, the percentage of INR values  $>2.5$  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 LVAD (HMII) 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.

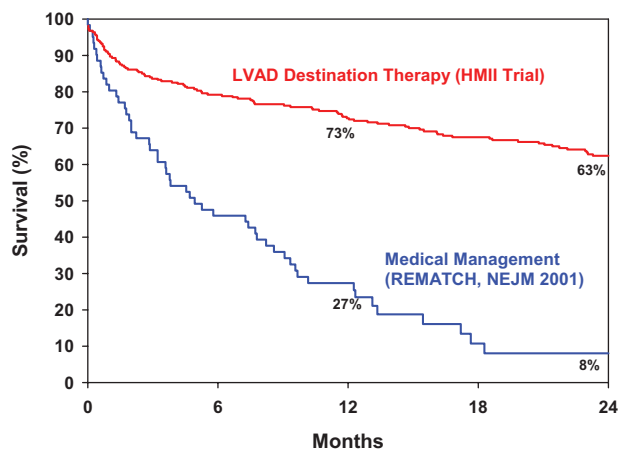
Improvements in outcomes are expected with increasing clinical experience with any new surgical therapy. However, in the case of the pulsatile HeartMate XVE LVAS, there was no improvement in survival between the original REMATCH study<sup>15</sup> and the most recent randomized DT trial<sup>2</sup> (1-year survival: 52% versus 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%<sup>6</sup> to 73%<sup>7</sup> during the trial and 85%<sup>8</sup> in the post-trial experience. Some of these

improvements observed can be attributed to better patient selection for the therapy, whereas others are possibly due to improved patient treatment before and after LVAD implant. These observations have resulted in an update of management guidelines for the HMII.<sup>16</sup> In the current study, most improvements are probably due to better postoperative and postdischarge patient treatment because the characteristics of patients selected were similar between the 2 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 HMII involved heparin in the immediate postoperative period, followed by warfarin with a target INR of 2.0–3.0, aspirin (81–100 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.<sup>17</sup> Additionally, patients with a HMII have been reported to have increased bleeding caused by acquired von Willebrand syndrome, which reduces platelet binding and activity.<sup>18,19</sup> Also, recent clinical experiences have shown that heparin may not be needed in transition to warfarin in the postoperative period.<sup>20</sup> Slaughter et al<sup>20</sup> demonstrated that there was no difference in thrombotic events between patients who were transitioned to warfarin on heparin and those who were not transitioned. Furthermore, patients who were not on heparin had fewer bleeding events.

Changes in recommendations of anticoagulation management have been highlighted in the updated patient treatment guidelines for HMII.<sup>16</sup> 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 that was most evident in the first 6 months of the early part of the trial (Figures 4 and 5). With respect to antiplatelet 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.<sup>2</sup> However, infection continues to be a significant source of morbidity and one of the primary reasons for prolonged hospital length of stay<sup>21</sup> 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 treatment, which eventually resulted in lower infection rates.



**Figure 6.** Inference of the survival benefit of current destination therapy with current continuous-flow left ventricular assist device (LVAD) compared with medical management from the REMATCH trial. HMII indicates HeartMate II.

From the results of this updated study in 281 DT patients, we can infer a magnitude of the survival benefit of continuous-flow LVAD compared with 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 HMII 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 HMII for long-term treatment of advanced heart failure, which are directly getting translated to improving clinical outcomes.

## Disclosures

Drs Park and Milano received research and training grants from Thoratec Corporation; Dr Rogers is a consultant for Thoratec Corporation; Dr Adamson conducted training and occasional speaking for Thoratec Corporation; Dr Ewald received a consulting fee from Thoratec Corporation; Drs Sundareswaran and Farrar are employees of Thoratec Corporation; and Dr Slaughter received research support from Thoratec Corporation.

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### CLINICAL PERSPECTIVE

Left ventricular assist devices (LVAD) have become an accepted treatment option for medically refractory advanced heart failure patients who are not eligible for heart transplantation. New-generation continuous-flow LVADs such as the HeartMate II (HMII) are smaller, quieter, and more durable than earlier generation pulsatile flow devices and are now the standard of care for long-term mechanical circulatory support. To evaluate if overall outcomes have improved with increasing clinical experience, survival, adverse events, and quality of life in HMII patients implanted under a continued access protocol (n=281) were compared with HMII patients implanted earlier as part of the primary data cohort (n=133). Improvement in outcomes included a significant reduction in serious adverse events such as hemorrhagic strokes, sepsis, device-related infection, bleeding, and cardiac arrhythmias, accompanied by an increasing trend in overall survival, compared with the early trial results. These improvements were attributed to better postoperative and postdischarge patient treatment because the baseline patient characteristics did not significantly change. Quality of life and functional capacity improved significantly in both groups. The promising findings of this study indicate that both clinicians and patients are benefiting from the increasing clinical experience associated with the use of a continuous-flow LVAD for long-term treatment of advanced heart failure.



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

Soon J. Park, Carmelo A. Milano, Antone J. Tatroles, Joseph G. Rogers, Robert M. Adamson, D. Eric Steidley, Gregory A. Ewald, Kartik S. Sundareswaran, David J. Farrar, Mark S. Slaughter and for the HeartMate II Clinical Investigators

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