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Continuous Flow Left Ventricular Assist Device Improves Functional Capacity and Quality of Life of Advanced Heart Failure Patients

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Objectives This study sought to assess the impact of continuous flow left ventricular assist devices (LVADs) on functional capacity and heart failure-related quality of life.

Background Newer continuous-flow LVAD are smaller and quieter than pulsatile-flow LVADs.

Methods Data from advanced heart failure patients enrolled in the HeartMate II LVAD (Thoratec Corporation, Pleasanton, California) bridge to transplantation (BTT) (n = 281) and destination therapy (DT) (n = 374) trials were analyzed. Functional status (New York Heart Association [NYHA] functional class, 6-min walk distance, patient activity scores), and quality of life (Minnesota Living With Heart Failure [MLWHF] and Kansas City Cardiomyopathy Questionnaires [KCCQ]) were collected before and after LVAD implantation.

Results Compared with baseline, LVAD patients demonstrated early and sustained improvements in functional status and quality of life. Most patients had NYHA functional class IV symptoms at baseline. Following implant, 82% (BTT) and 80% (DT) of patients at 6 months and 79% (DT) at 24 months improved to NYHA functional class I or II. Mean 6-min walk distance in DT patients was 204 m in patients able to ambulate at baseline, which improved to 350 and 360 m at 6 and 24 months. There were also significant and sustained improvements from baseline in both BTT and DT patients in median MLWHF scores (by 40 and 42 U in DT patients, or 52% and 55%, at 6 and 24 months, respectively), and KCCQ overall summary scores (by 39 and 41 U, or 170% and 178%).

Conclusions Use of a continuous flow LVAD in advanced heart failure patients results in clinically relevant improvements in functional capacity and heart failure-related quality of life. (J Am Coll Cardiol 2010;55:1826–34) © 2010 by the American College of Cardiology Foundation

Left ventricular assist devices (LVADs) are becoming a standard therapeutic option for patients with advanced heart failure who are failing maximal medical treatment (1–12). Newer generation LVADs have been developed with continuous flow, rotary pump technology and are smaller and quieter than older pulsatile volume displacement LVADs, with the capability of providing similar outputs of up to 10 l/min (9–11). Continuous flow LVADs have been demonstrated to improve morbidity and mortality in critically ill patients awaiting transplantation while simultaneously reducing adverse events (9–11).

Previous studies on pulsatile flow LVADs have demonstrated significant improvements in quality of life measures and New York Heart Association (NYHA) functional class over time (5,13–17). Initial results from the continuous flow

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HeartMate II LVAD (Thoratec Corporation, Pleasanton, California) trials also indicate improvements in quality of life and functional status (9–11,18) and stability or improvements in domains of neurocognitive function (19). However, a detailed analysis in a large number of patients that describes the impact of continuous blood flow with reduced pulse pressure on long-term patient exercise performance and quality of life metrics has not been performed. In this study, we report the impact of a continuous flow LVAD in over 650 patients with advanced heart failure on quality of life and functional capacity for up to 24 months of circulatory support.

Methods

The HeartMate II LVAD is a continuous flow device consisting of an internal axial-flow blood pump with a percutaneous lead that connects the pump to an external system controller and power source (Fig. 1). Data presented in this analysis are from the HeartMate II bridge to transplant (BTT) and destination therapy (DT) clinical trials that were conducted between 2005 and 2009 at 38 centers in the U.S. (9–11). The authors had access to the primary data and attest to its accuracy. The HeartMate II studies were conducted in compliance with U.S. Food and Drug Administration (FDA) regulations for good clinical practices. The protocols were approved by the FDA and each participating center's institutional review board.

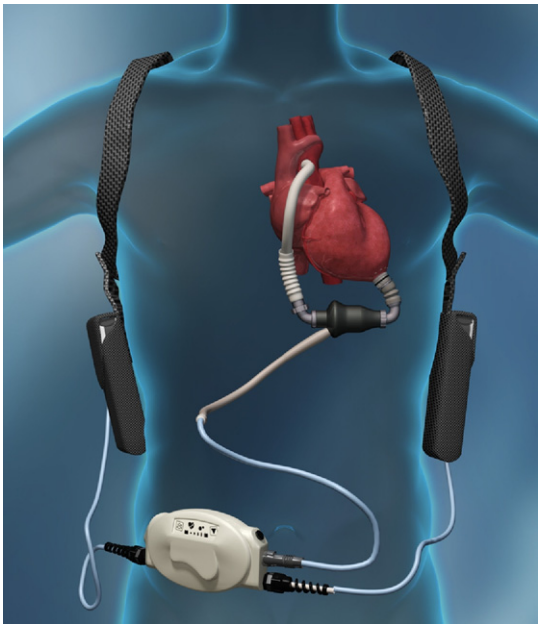

Figure 1 HeartMate II Continuous Flow LVAD

Blood exits through the left ventricular apex and into the left ventricular assist device (LVAD), which pumps throughout cardiac diastole and systole into the ascending aorta. The LVAD pump is placed within the abdominal wall or peritoneal cavity. A percutaneous lead connects the LVAD to an electronic controller and battery packs, which are worn on a belt and shoulder holster, respectively.

Study subjects. Patients enrolled in the BTT trial had NYHA functional class IV heart failure symptoms and were listed as high priority for transplantation (United Network for Organ Sharing status 1A or 1B). Patients with NYHA functional classes IIIB and IV heart failure who were ineligible for heart transplantation and refractory to optimal medical management were considered for enrollment in the DT trial. Exclusion criteria for both the trials included severe renal, pulmonary, or hepatic dysfunction, active uncontrolled infection, a mechanical aortic valve, aortic insufficiency, an aortic aneurysm, other mechanical circulatory support (except an intra-aortic balloon pump [IABP]), and technical obstacles thought by the investigator to pose excessive surgical risk. Detailed characteristics and inclusion/exclusion criteria of each of these patient cohorts have been published elsewhere (9–11). All participating patients provided written informed consent.

Abbreviations and Acronyms

CSS = clinical summary score
IABP = intra-aortic balloon pump
KCCQ = Kansas City Cardiomyopathy Questionnaire
LVAD = left ventricular assist device
METS = metabolic equivalent task score
MLWHF = Minnesota Living With Heart Failure
NYHA = New York Heart Association
OSS = overall summary score

Baseline and post-implant assessments. Assessments of functional status and quality of life were obtained in patients prior to LVAD implant (baseline) and at 1, 3, and 6 months post-implant for those enrolled in the BTT trial, and at 1, 3, 6, 12, 18, and 24 months for patients in the DT trial.

Table 1 Pre-Operative Baseline Characteristics in BTT and DT Patients

Parameter	BTT (n = 281)	DT (n = 374)	p Value
Age, yrs	50 ± 13	63 ± 12	<0.001
Female, %	67 (24%)	102 (27%)	0.322
Ischemic etiology of heart failure, %	121 (43%)	217 (58%)	<0.001
LVEF, %	16.3 ± 6.5	17.1 ± 5.8	0.025
CI, l/min/m^2	2.1 ± 0.6	2.1 ± 0.6	0.889
PCWP, mm Hg	25.4 ± 7.9	23.9 ± 8.3	0.021
Systolic BP, mm Hg	98.1 ± 15.0	102.1 ± 15.1	<0.001
BUN, mg/dl	30.4 ± 17.1	34.4 ± 21.3	0.023
Creatinine, mg/dl	1.4 ± 0.5	1.5 ± 0.6	0.040
Total bilirubin, mg/dl	1.3 ± 0.9	1.3 ± 1.0	0.603
ALT, U/l	106 ± 278	44 ± 69	<0.001
Na, mmol/l	134 ± 5	135 ± 5	0.002
CRT	135 (48%)	268 (72%)	<0.001
Intravenous inotropes	252 (90%)*	289 (77%)	0.001
IABP	126 (45%)	78 (21%)	<0.001

*10% intolerant due to arrhythmias.

ALT = alanine aminotransferase; BP = blood pressure; BTT = bridge to transport; BUN = blood urea nitrogen; CI = cardiac index; CRT = cardiac resynchronization therapy; DT = destination therapy; IABP = intra-aortic balloon pump; LVEF = left ventricular ejection fraction; Na = serum sodium; PCWP = pulmonary capillary wedge pressure.

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NYHA functional class at each time period was assessed independently by a physician, nurse, or other trained medical staff not directly involved with the patient's care at that time. Submaximal exercise performance was measured using the 6-min walk test. Patients unable to walk at any time period due to a medical condition (i.e., IABP in place; in intensive care unit on inotropes; orthopedic limitations) and patients who refused to walk were excluded from this analysis.

Activity levels were assessed using metabolic equivalent task score (METs) in which patients were asked to describe their highest activity level during the reporting period, with scores ranging from very low (<1 METS = bedridden, unable to care for self, unable to participate in any physical activity), moderate (2 to 4 METS = walking 2 to 3 mph, light gardening, vacuuming or mopping the floor, golfing, painting walls), to very high (>6 METS = dancing, climbing stairs, stationary cycling [>10 mph], heavy shoveling) (20).

Heart failure-related quality of life was assessed with the Minnesota Living With Heart Failure Questionnaire (MLWHF) (21,22) and Kansas City Cardiomyopathy Questionnaire (KCCQ) (23). The MLWHF questionnaire assesses the impact of heart failure and its treatment on key physical, emotional, social, and mental dimensions of quality of life. The KCCQ quantifies physical function, symptoms (frequency, severity, and recent change), social function, self-efficacy, and knowledge, and quality of life. An overall summary score (OSS) is derived by combining scores in each domain. A clinical summary score (CSS) is derived by combining the physical function and symptoms scores. For both KCCQ summary scores, a higher value represents

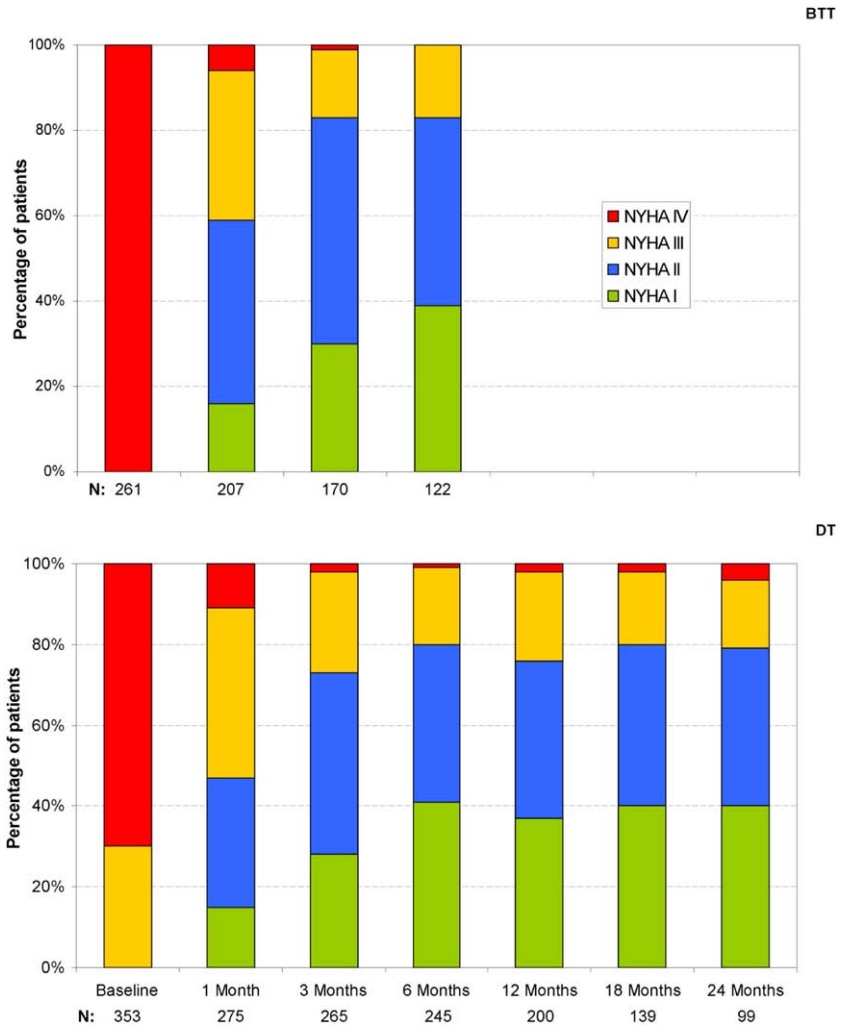

Figure 2 **Changes in Functional Class Following LVAD**

New York Heart Association (NYHA) functional class was determined by an independent clinician at the time points shown in the bridge to transplant (BTT) and destination therapy (DT) trials. Study inclusion criteria required NYHA functional class III to IV symptoms at baseline. NYHA functional class improvements were statistically significant in both trials ($p < 0.001$).

a better quality of life, whereas a lower score reflects improved quality of life with the MLWHF questionnaire.

Statistical analysis. Differences between baseline characteristics of BTT and DT patients were determined for descriptive purposes only, with independent samples *t* test for continuous variables or the Fisher exact test for categorical variables. No adjustments were made on functional status or quality of life data based on baseline differences between cohorts. For continuous variables of the 6-min walk test, MLWHF, and KCCQ, linear mixed effects modeling was used to determine statistical significance. Post hoc comparisons were performed using the Scheffe test. For categorical variables (NYHA functional class, activity levels), mixed effects ordinal regression was performed to test for significant changes over time. The level of statistical significance was set at $p < 0.05$. All statistical comparisons are 2-sided. Statistical analyses were done using Systat (Cranes Software, Chicago, Illinois) and MIXOR (24).

Results

Baseline clinical characteristics of patients are shown in Table 1. The BTT patients were younger and more likely to be treated with intravenous inotropic agents or an IABP, whereas the DT patients had a higher systolic blood pressure and worse renal function. More than 75% of patients in both groups were receiving intravenous inotropes at baseline, and 45% of patients in the BTT and 21% in the DT trials were supported with an IABP at study enrollment. Cardiac resynchronization therapy (CRT) was used in 48% and 72% of the BT and DT patients, respectively. The number of patients available for testing varied at each time interval because of transplantation, death, study withdrawal, device explantation, availability of study personnel, and scheduling. Overall survival and outcomes associated with the BTT and DT trials have been published previously (9–11).

Functional status. NYHA FUNCTIONAL CLASS. Figure 2 shows the change in NYHA functional class over time for the BTT and DT cohorts. At baseline, most patients had NYHA functional class IV symptoms, and after 1 month of support, 59% (BTT) and 47% (DT) of patients improved to NYHA class I or II, increasing further after 6 months of support to 82% (BTT) and 80% (DT). Approximately 80% of DT patients remained in NYHA functional class I or II from 6 through 24 months. With respect to their baseline scores, patients achieved highly significant improvement in NYHA functional class at all study intervals for both the study groups ($p < 0.001$). There was no significant difference in the improvements seen in NYHA class between BTT and DT patients.

6-MIN WALK TEST. At baseline, a relatively small percentage of patients in both the BTT (14%) and DT (34%) cohorts were able to perform the 6-min walk test. For patients who performed the test, average baseline 6-min walk distance was 214 ± 125 m (BTT) and 204 ± 150 m (DT), which increased significantly at 6 months to 372 ±

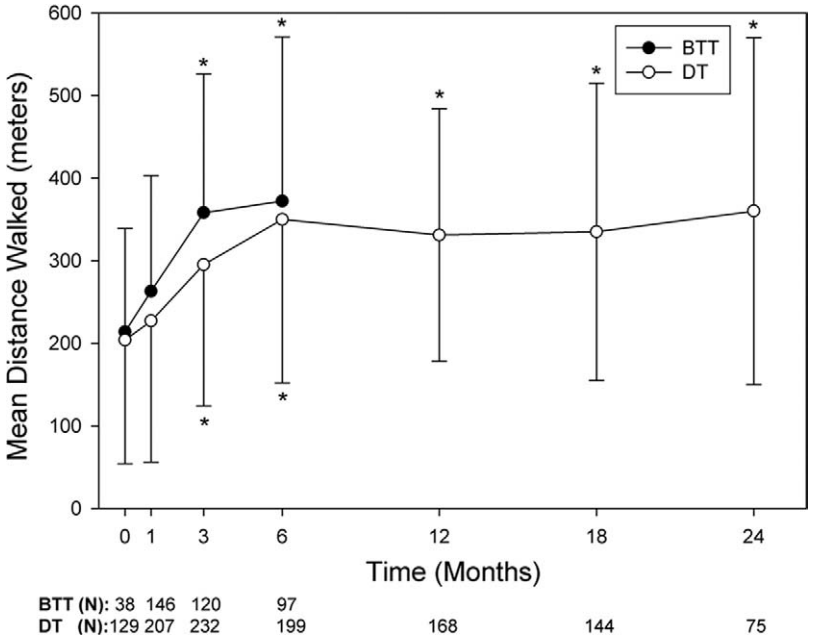

Figure 3 Submaximal Exercise Performance After LVAD

Mean 6-min walk distances in the BTT and DT trials are shown over time. Ascertainment of baseline 6-min walk distance was limited to patients able to ambulate. The number of observations (n) at each time point is shown at the bottom of the figure. *$p < 0.05$ compared with baseline. LVAD = left ventricular assist device; other abbreviations as in Figure 2.

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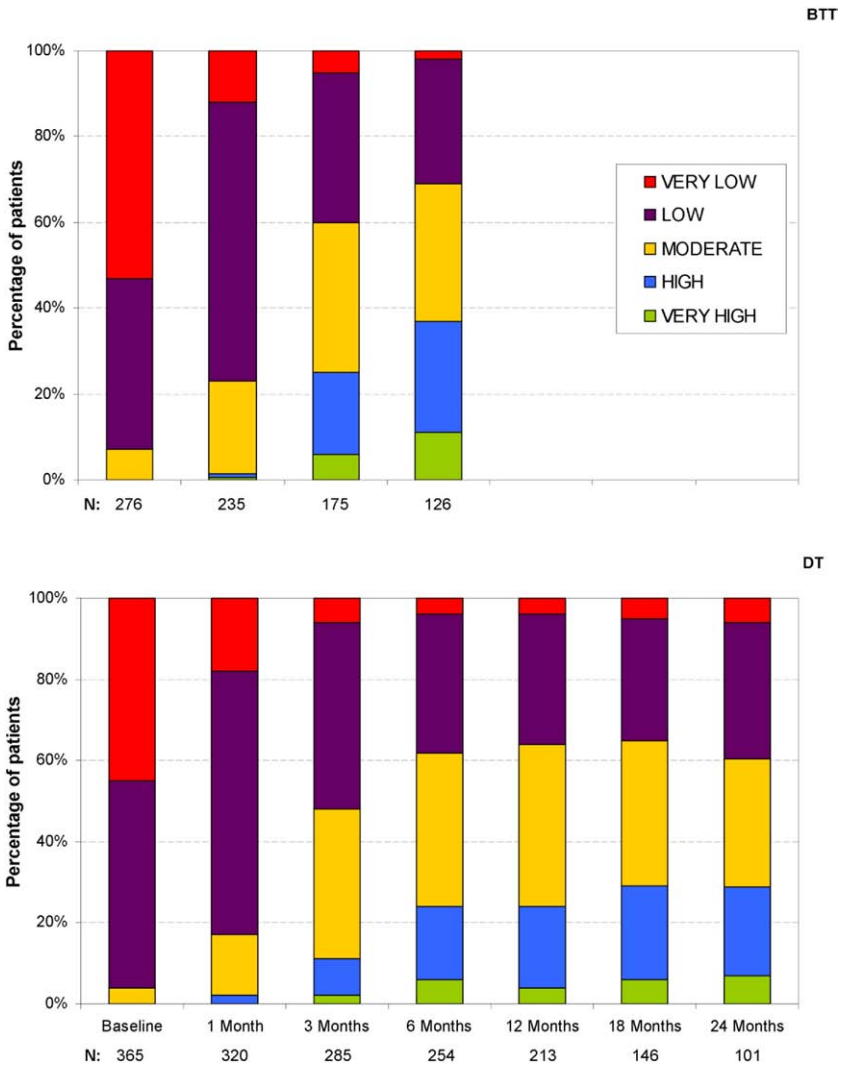

Figure 4 **Patient-Reported Exercise Ability Following LVAD**

Serial assessment of metabolic equivalent task score (METs). At baseline, >90% of patients in both trials described their level of function as low or very low. At 6 months, approximately two-thirds of patients described their level of function as moderate to very high ($p < 0.001$ vs. baseline). LVAD = left ventricular assist device.

199 m and 350 ± 198 m for BTT and DT, respectively (Fig. 3). The 6-min walk distance was maintained throughout the follow-up period in the DT patients and was 360 ± 210 m at 24 months. Overall, there was a statistically significant improvement over time at all test intervals for both study groups (Fig. 3). In DT patients, the mean walk distance from baseline to 24 months increased by more than 150 m.

PATIENT ACTIVITY SCORES. Figure 4 shows the percentage of patients with each activity level at each time point. At baseline, 93% of patients in the BTT group, and 96% of the patients in the DT group described their level of activity as either low or very low. By 6 months, 68% of patients in the BTT group and 62% in the DT group described their activity levels as moderate, high, or very high, an improvement that was highly significant ($p < 0.001$). After 6 months, the level of improvement stabilized in the DT cohort, and 60% of the patients described their activity levels as moderate, high, or very high at 24 months.

QUALITY OF LIFE QUESTIONNAIRES. MLWHF scores decreased over time, indicating an improvement in quality of life (Fig. 5, Table 2). When compared with baseline scores in patients with paired comparisons, highly significant ($p < 0.001$) median improvement in scores of −10 and −13 points were seen at 1 month in the BTT and DT groups, followed by continued improvements of −29 and −40 points at 6 months of support. The median percent improvement at 6 months for the BTT and DT groups were 38% and 52%, respectively. At 24 months, there was a median improvement of −42 points (55%) compared with baseline.

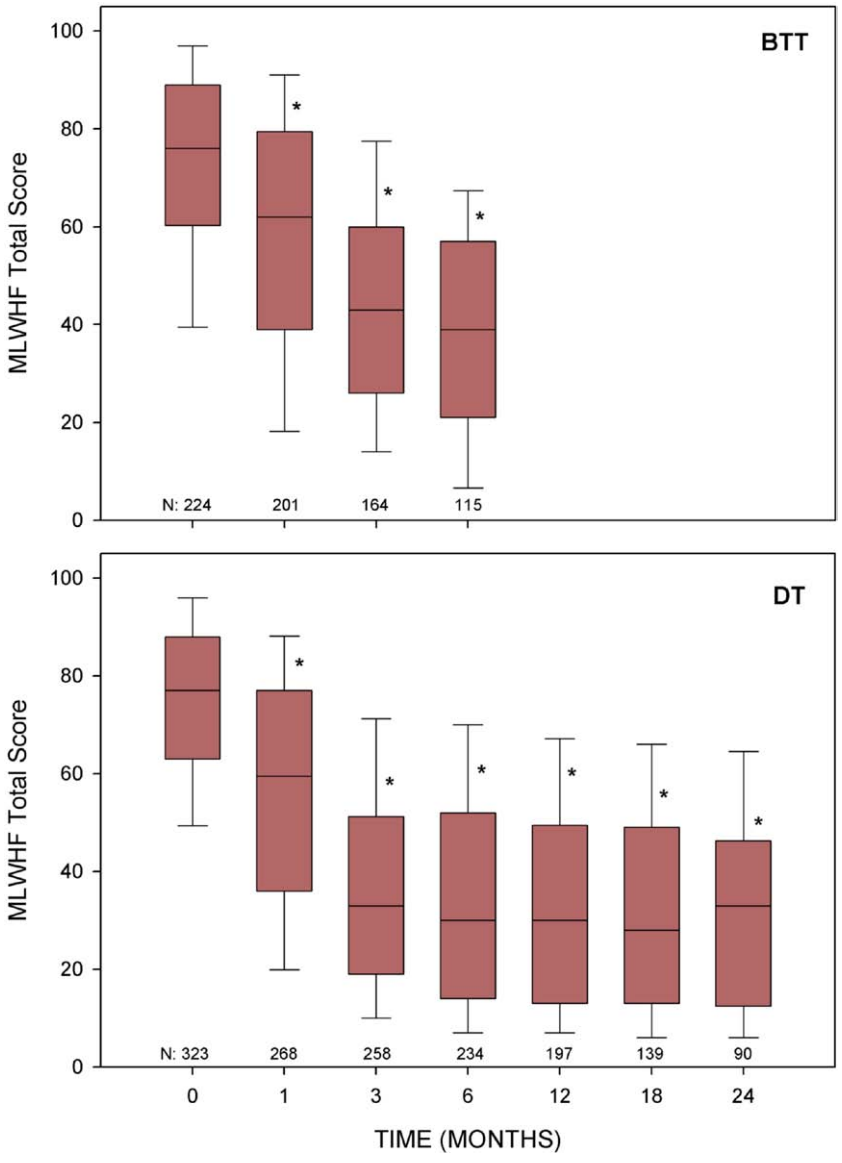

Figure 5 **Changes in Quality of Life: MLWHF**

Changes in quality of life assessed with the Minnesota Living With Heart Failure (MLWHF) Questionnaire are shown. Lower values signify improved quality of life. **Bars** indicate 25th, 50th, and 75th percentiles, **whiskers** indicate 5th and 95th percentiles. *$p < 0.05$ compared with baseline.

KCCQ overall summary and clinical summary scores also improved during HeartMate II support (Fig. 6, Table 2). The median KCCQ OSS showed significant early improvements by 14 and 16 points at month 1 for BTT and DT patients compared with baseline, with 28 and 39 point improvements at 6 months of support. After 6 months, the KCCQ scores remained stable with a median improvement in DT patients of 41 points at 24 months compared with baseline. Similar improvements were observed in the KCCQ CSS. At 6 months post-implant, 79% of BTT and 92% of DT patients with paired data had achieved a clinically meaningful improvement of >5 points in their KCCQ OSS compared with baseline. Similar results were found for the KCCQ CSS.

Discussion

The current study demonstrates that patients with advanced heart failure who have marked functional limitations and impaired quality of life derive significant improvements in submaximal exercise performance and heart failure-related quality of life following implantation of a continuous flow LVAD. Similar improvements were seen in both the BTT and DT patients, 2 overlapping populations typically defined by age and severity of comorbidities. Although trial

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Table 2 Quality of Life Improvements Over Time in Patients Implanted With the HMII

	HMII BTT				HMII DT			
		Paired Changes				Paired Changes		
Month	n	Mean ± SD	Median [25th, 75th]	% Improvement of Median	n	Mean ± SD	Median [25th, 75th]	% Improvement of Median
MLWHF								
1	167	−12 ± 27	−10 [−28, 4]	13%	241	−17 ± 31	−13 [−40, 4]	17%
3	126	−24 ± 31	−30 [−47, −4]	39%	231	−35 ± 28	−37 [−58, −17]	48%
6	87	−28 ± 28	−29 [−50, −9]	38%	209	−39 ± 27	−40 [−60, −20]	52%
12	0	—	—	—	177	−39 ± 30	−41 [−62, −17]	53%
18	0	—	—	—	126	−39 ± 25	−42 [−57, −22]	55%
24	0	—	—	—	82	−41 ± 25	−42 [−57, −20]	55%
KCCQ OSS								
1	172	13 ± 25	14 [−3, 29]	54%	242	17 ± 26	16 [−1, 35]	70%
3	132	22 ± 26	20 [9, 42]	77%	232	35 ± 24	34 [19, 53]	148%
6	90	27 ± 28	28 [7, 45]	108%	211	39 ± 24	39 [20, 58]	170%
12	0	—	—	—	181	40 ± 25	42 [24, 61]	183%
18	0	—	—	—	129	41 ± 24	38 [22, 61]	165%
24	0	—	—	—	89	42 ± 23	41 [25, 60]	178%
KCCQ CSS								
1	170	12 ± 27	11 [−6, 31]	30%	240	15 ± 27	13 [−3, 34]	41%
3	132	21 ± 28	21 [4, 42]	57%	231	32 ± 25	32 [14, 50]	100%
6	90	25 ± 31	24 [8, 43]	65%	210	37 ± 25	36 [17, 55]	113%
12	0	—	—	—	181	36 ± 28	39 [18, 57]	122%
18	0	—	—	—	129	37 ± 27	34 [18, 61]	106%
24	0	—	—	—	89	38 ± 26	35 [20, 55]	109%

Values are the mean ± SD and median [25th, 75th percentiles] of paired changes at each time point compared with baseline. Also shown are the percent improvements of the median from baseline.
CSS = clinical summary score; HMII = HeartMate II; KCCQ = Kansas City Cardiomyopathy Questionnaire; MLWHF = Minnesota Living With Heart Failure; OSS = overall summary score.

design limited follow-up to 6 months in the BTT cohort, the DT trial allowed more prolonged observation of changes in patient functionality and quality of life. The early improvements in exercise performance and quality of life demonstrated in both patient groups were sustained and showed no evidence of decline through 2-year follow-up.

The current report is the largest study of advanced heart failure patients with serial measurement of functional capacity and quality of life metrics following a mechanical intervention. The poor pre-implant exercise performance and quality of life scores despite optimal medical and electrical therapies, including CRT when appropriate, highlight the limitations of currently utilized treatments for patients with stage D heart failure. Recent studies have documented 1-year survival rates of 73% in BTT patients (10) and 1- and 2-year survival rates of 68% and 58% in DT patients supported with a continuous flow LVAD (11). However, a majority of patients with advanced heart failure express a strong desire for improvements in quality of life and functionality, even at the expense of longevity (25,26). The totality of data from the HeartMate II trials suggests that these patients who have a predictably high short-term mortality and symptoms with minimal activity or at rest may be able to achieve both mortality reduction and improved quality of life following treatment with a continuous flow LVAD. Therapies targeted to the stage D heart failure population must focus on patient-centric outcomes that include reduction of symptom burden and improved ability to perform the activities of daily living. This study establishes a benchmark against which other medical and device therapies can compare.

The 6-min walk test is an accepted method for assessing functional capacity that has good reproducibility, is well tolerated, and is very relevant to daily activities (27). This test has been used extensively in heart failure clinical trials (28). The relative improvements in exercise performance seen with the continuous flow LVAD can be put into perspective by comparison to the outcomes of patients enrolled in CRT trials. A prior study supporting the use of CRT in patients with NYHA functional class III to IV heart failure symptoms established that a 39-m improvement in 6-min walk distance can be considered clinically meaningful (29). A retrospective analysis of patients with NYHA functional class IV symptoms treated with CRT from the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure) trial demonstrated a statistically significant 46-m increase in 6-min walk distance with 78% experiencing ≥1 functional class improvement (30). In contrast, LVAD-treated patients in this study who were able to complete a 6-min walk test prior to device implantation had a 146-m increase in mean walk distance at 6 months (DT group), and more than 80% of patients had ≥2 functional class improvements (DT group). Additionally, most patients reported significant increases in daily functional capabilities as indicated by moderate activity levels or higher based upon estimated METs.

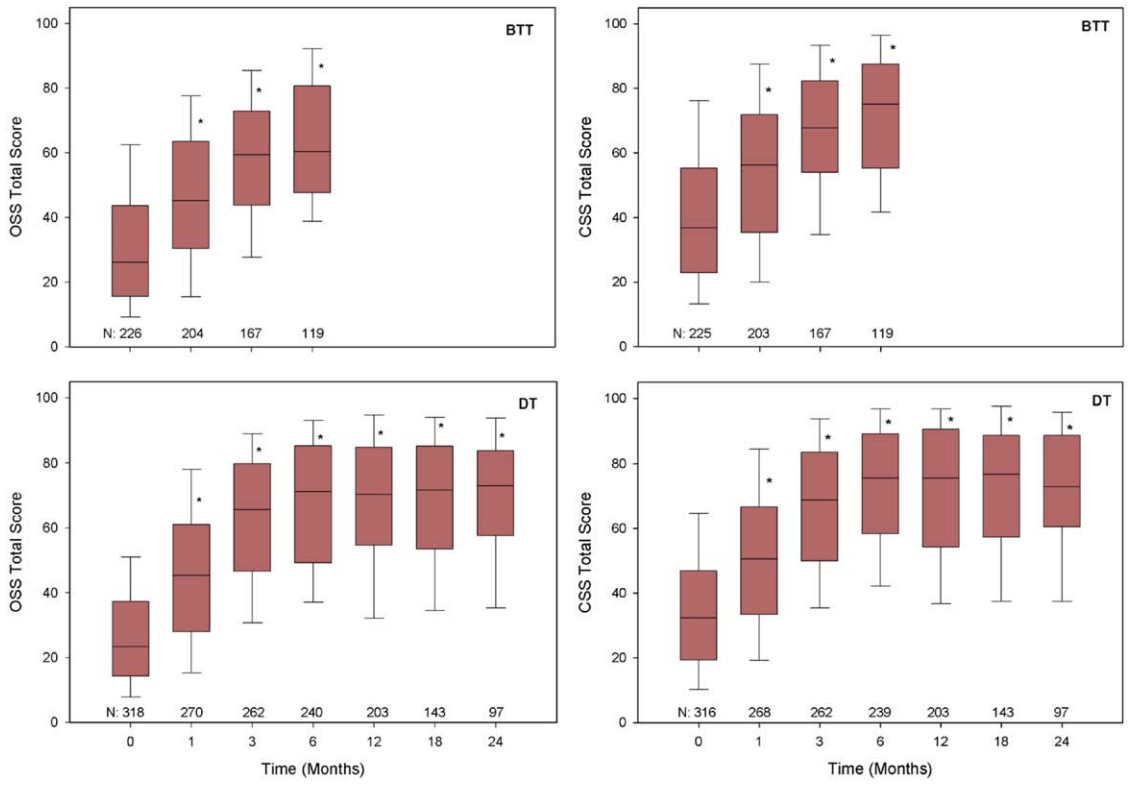

Figure 6 **Changes in Quality of Life Assessed With the KCCQ**

Kansas City Cardiomyopathy Questionnaire (KCCQ) scores versus left ventricular assist device support duration are shown. **Bars** indicate 25th, 50th, and 75th percentiles, **whiskers** indicate 5th and 95th percentiles. *$p < 0.05$ compared with baseline. CSS = clinical summary score; OSS = overall summary score.

The first-generation pulsatile LVADs delivered blood flow in a manner similar to the native heart. Once the device was full, pump systole resulted in a normal stroke volume of 70 to 80 ml. Previous studies with these devices have shown improved exercise capacity (31,32), functional status, and/or quality of life with LVAD support relative to medical therapy (5,14) and in serial testing over time (13,15–17). A unique aspect of the continuous flow LVADs is reduction of the pulse pressure that is dependent upon the speed at which the device is run. At higher speeds, the device can unload the ventricle completely, with corresponding reductions in pulse pressure. In clinical practice, the continuous flow LVADs are commonly set at speeds that provide 5 to 6 l of flow with a detectable, but reduced, pulse pressure. Haft et al. showed substantially reduced pulse pressure with mean systolic and diastolic blood pressures of 98/77 mm Hg in patients with continuous flow LVADs compared with 116/64 mm Hg for patients with pulsatile flow LVADs after 3 months of support, but no difference in exercise capacity (31). The impact of long-term reduced pulsatility on peripheral muscle function and subsequent functional capacity remains largely unexplored. Coupled with the demonstrated improvements in exercise performance, it may be reasonably assumed that alterations in flow characteristics typically seen with continuous flow LVADs do not negatively impact peripheral muscle function, at least through the first 24 months of support.

A 5-point change in both the MLWHF score and the KCCQ has been previously determined to be clinically meaningful (21–23,33). Both patient cohorts in our analysis experienced an early 10-point improvement in median MLWHF score 1 month after LVAD implantation, with further improvement in MLWHF scores observed throughout the observation periods. In fact, at 24 months, DT patients had a 42-point paired improvement in quality of life score assessed by this tool, and a 41-point paired improvement using the KCCQ instrument.

One limitation of this study is that both MLWHF and KCCQ represent heart failure-related quality of life measures, whereas a wider range of domains of quality of life such as those reported by Grady et al. (13) would provide a more complete assessment. Other limitations include a variable number of patients studied at each time interval due to such factors as death, transplantation, staff availability, or scheduling, and thus there could be ascertainment bias due to exclusion of sick patients. This may be partially offset by simultaneous exclusion of healthy patients who underwent transplantation. Paired analyses of improvements were per-

formed where possible and confirm findings with the overall population as a whole. Also, there are incomplete data on the 6-min walk test related to exclusion of patients who were unable to walk at baseline due to medical issues, most of which were related to the severity of heart failure, including bedridden condition, presence of an IABP, or inotropes. Exclusion of these patients from the analysis may underestimate the overall improvement associated with the therapy. An analysis of the potential effects of patients with missing data is provided in the Online Appendix.

Conclusions

HeartMate II LVAD support in both the bridge to transplant and destination therapy applications results in early, sustained, and clinically meaningful improvements in functional capacity and heart failure-related quality of life.

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Key Words: HeartMate II ■ ventricular assist devices ■ quality of life ■ functional status ■ continuous flow.

APPENDIX

For a supplementary table, please see the online version of this article.