

Outcomes of Adult Patients with Small Body Size Supported with a Continuous-Flow Left Ventricular Assist Device

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There is insufficient data on patients with small body size to determine if this should be considered a risk factor for continuous-flow left ventricular assist device (CF-LVAD) support. We sought to evaluate survival outcomes, adverse events, and functional status of CF-LVAD patients with body surface area (BSA) $<1.5 \text{ m}^2$ in a large national registry. Adults with BSA $<1.5 \text{ m}^2$ ($n = 128$) implanted with a HeartMate II (HMII)-LVAD from the Interagency Registry for Mechanically Assisted Circulatory Support registry from April 2008 to December 2012 formed this cohort. Outcomes were compared with HMII bridge to transplant (BTT) and destination therapy (DT) post approval studies. The majority of patients were female ($n = 106$, 83%). A total of 64% ($n = 82$) were implanted for BTT and 36% ($n = 46$) for DT. The median BSA (range) was 1.44 (1.19–1.49) and 1.45 (1.25–1.49) m^2 for BTT and DT, respectively. Overall survival 1 year post implant was 81% \pm 5% for BTT and 84% \pm 6% for DT. The most common adverse events for BTT and DT patients were bleeding (0.91, 0.88 events/patient year) and driveline infection (16%, 0.28 events/patient year). Six months post implantation, 87% of BTT and 77% of DT patients were New York Heart Association functional class I or II. Post implant survival, functional status improvement, and adverse event profile for adult BTT and DT HMII patients with BSA $<1.5 \text{ m}^2$

are favorable and comparable with outcomes published in the overall patient population. *ASAIO Journal* 2016; 62:646–651.

Key Words: LVAD, BSA, BMI, INTERMACS, HeartMate II

The landscape in the treatment of advanced heart failure is evolving rapidly with the increased use of continuous-flow left ventricular assist devices (CF-LVADs) as a bridge to transplant (BTT) or as destination therapy (DT). In the latest Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) 7th annual report, there have been more than 15,000 durable Food and Drug Administration (FDA)-approved devices implanted since June 2006.¹ The International Society of Heart and Lung Transplantation reports that the percentage of patients bridged with a LVAD at the time of heart transplantation has increased from $<20\%$ in 2000 to more than 35% in 2011.² Moreover, there is increased utilization of these devices as long-term permanent therapy or DT for advanced heart failure now accounting for up to 40% of all indications for CF-LVAD implantation in recent years.³ Outcomes in recent post FDA approval studies have been excellent, with 85% survival of those remaining on CF-LVAD support 1 year post implant for BTT patients and 74% for DT patients.^{4,5}

Compared with the earlier technology of pulsatile displacement pumps, CF-LVADs are smaller in size and can be implanted in the more restrictive anatomy of small patients. However, there is a paucity of data on the use and safety of CF-LVADs in adult patients with a small body surface area (BSA) $<1.5 \text{ m}^2$. The HeartMate II clinical trial included a small body size cohort of 10 patients which indicated similar outcomes in patients with BSA $<1.5 \text{ m}^2$ and those more than 1.5 m^2 .⁶ To further address and clarify the use of CF-LVADs in adult patients with a small BSA in the post approval era, we sought to evaluate the survival outcomes, adverse events, and functional status of patients with BSA $<1.5 \text{ m}^2$ implanted with a CF-LVAD in a large national registry.

Methods

Patients

The INTERMACS registry was queried to identify all adult patients ≥ 18 years of age with a BSA $<1.5 \text{ m}^2$ who were implanted with the HeartMate II CF-LVAD (HMII, Thoratec Corporation, Pleasanton, CA) between April 2008 and December 2012 ($n = 128$) for BTT ($n = 82$) or DT ($n = 46$) indications. Outcomes were compared with the HMII BTT (April to August 2008; $n = 169$) and DT (January to September 2010; $n = 247$) post approval studies (PASs).

Data Collection

This was a retrospective registry study using the INTERMACS database. Data entry into the INTERMACS database

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Table 1. Baseline Characteristics: Small BSA Cohort

Characteristic	BTT (n = 82)	DT (n = 46)
Age (year)		
<40	20 (24%)	2 (4%)
40–59	29 (35%)	9 (19%)
≥60	33 (40%)	35 (76%)
Female sex (%)	66 (80%)	40 (87%)
Race		
White	51 (62%)	30 (65%)
Black	15 (18%)	1 (2%)
Asian/American Indian	6 (7%)	9 (20%)
Unknown/other	10 (13%)	6 (13%)
INTERMACS profiles		
Profile 1	18 (22%)	5 (11%)
Profile 2–3	52 (64%)	29 (63%)
Profile 4–7	10 (12%)	12 (26%)
Ischemic etiology (%)	26 (32%)	20 (43%)
NYHA class IV (%)	62 (76%)	39 (85%)
Body surface area (m ²) (median [range])	1.44 [1.19–1.49]	1.45 [1.25–1.49]
Weight (kg)	47 [35–53]	49 [39–54]

BSA, body surface area; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.

is voluntary and is specified by each participating center. The adverse events definitions and variables analyzed may be accessed via the INTERMACS website.⁷

Statistical Analysis

Continuous variables are presented as mean \pm SD or median (range). Categorical variables are presented as proportions. Survival, adverse events, and quality of life were compared with the HMII BTT⁴ and DT⁵ PAS. Survival was evaluated using the Kaplan–Meier method. Comparison of survival between two groups was performed using the log-rank test. Adverse events are presented as both percentages and event rates (events per patient

year of support; eppy). Comparisons of adverse event rates were performed using Cochran–Mantel–Haenszel statistics. All statistical comparisons were two sided with a significance level at $p < 0.05$. Statistical analyses were performed with SigmaPlot (Cranes Software, Chicago, IL) and SAS (SAS Institute, Inc., Cary, NC).

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the small BSA < 1.5 m² cohort stratified by BTT and DT. The most striking demographic characteristic unique to this patient population is that the majority of the patients (80% BTT and 87% DT) were female. The majority of patients were implanted as INTERMACS profile 2–3 (64% BTT and 63% DT) and New York Heart Association (NYHA) Class IV (76% BTT and 85% DT). The median (range) BSA was 1.44 m² (1.19–1.49) and 1.45 m² (1.25–1.49) for BTT and DT patients, respectively. Age was greater in the DT group with 76% at least 60 years old compared with 40% for BTT. **Tables 2 and 3** show the baseline characteristics of the HMII BTT and DT PAS cohorts, respectively. Females made up 22% and 17% of the BTT and DT PAS cohorts, respectively. The median BSA was 2.03 ± 0.25 and 2.01 ± 0.29 m² for the BTT and DT PAS cohorts, respectively.

Outcomes

Survival. The survival of the small BSA cohort was compared with the survival of the HMII BTT⁴ and DT⁵ PASs (**Figures 1 and 2**). For the BTT population, the 6 month and 1 year post implant survival of the small BSA cohort was $84\% \pm 4\%$ and $81\% \pm 5\%$, respectively, which were similar to and not statistically different from the 6 month and 1 year post implant survival in the post approval BTT population ($90\% \pm 2\%$ and $84\% \pm 3\%$, respectively; $p = 0.367$). For the DT population, the 1 and 2 year post implant survival of the small BSA cohort was $84\% \pm$

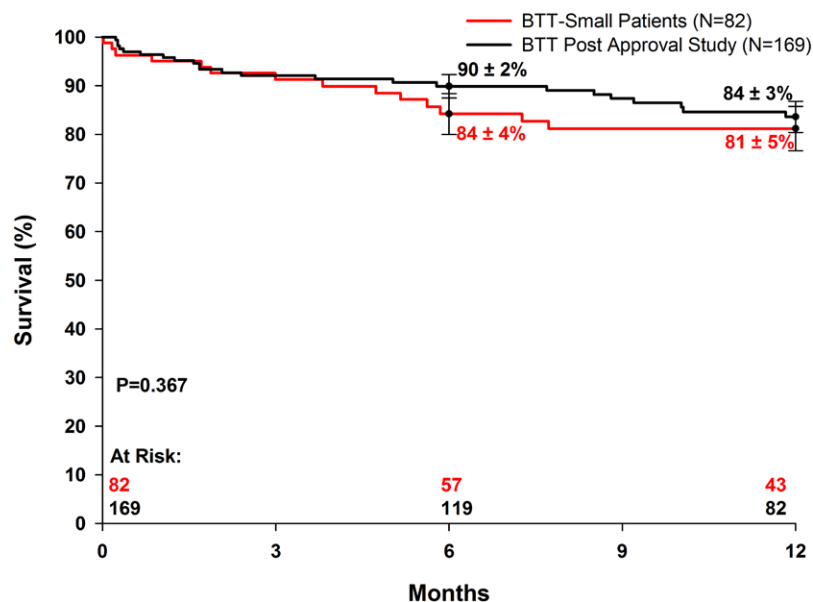


Figure 1. Kaplan-Meier survival for small BSA BTT patients compared to post approval BTT study. BSA, body surface area; BTT, bridge to transplant.

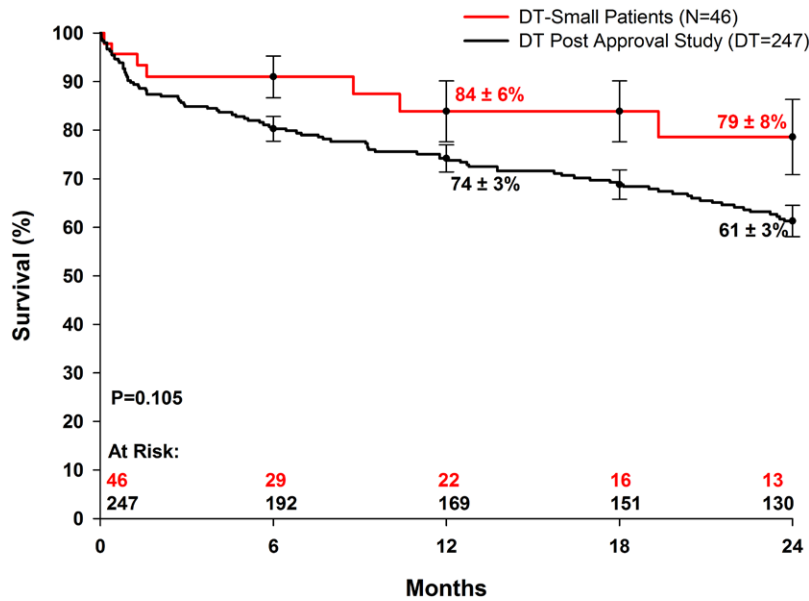


Figure 2. Kaplan-Meier survival for small BSA DT patients compared to postapproval DT study. BSA, body surface area; DT, destination therapy. full color online

6% and 79% ± 8%, respectively, and trended higher but was not statistically different from the 1 and 2 year post implant survival in the post approval DT population (74% ± 3% and 61% ± 3%, respectively; *p* = 0.105).

Adverse Events. The adverse event rates for the small BSA cohort are similar to the BTT and DT post approval patients (Tables 4 and 5, respectively). However, in the BTT population, bleeding was significantly lower in the small BSA cohort (0.91 vs. 1.44 eppy; *p* = 0.010). In DT patients, hemolysis occurred more frequently in the small BSA patients (0.16 vs. 0.06 eppy; *p* = 0.014).

Functional Status. Both BTT and DT small BSA patients had a marked improvement in NYHA Classification. Before implant, no patients reported NYHA Class I/II symptoms. At

6 months post implant, more than 75% of small BSA patients had improved to NYHA class I/II with sustained improvement through 12 months (Figure 3A, B).

Discussion

This study represents the largest cohort of adult patients with a BSA < 1.5 m² implanted with a CF-LVAD and support the use of CF-LVAD therapy in this patient population.

The post implant survival of small BSA patients are comparable with the published HMII post approval BTT and DT studies where the mean BSA was 2.03 ± 0.25 and 2.01 ± 0.29 m², respectively.^{4,5} The post implant survival of the small BSA BTT cohort was 84% ± 4% and 81% ± 5% at 6 months and

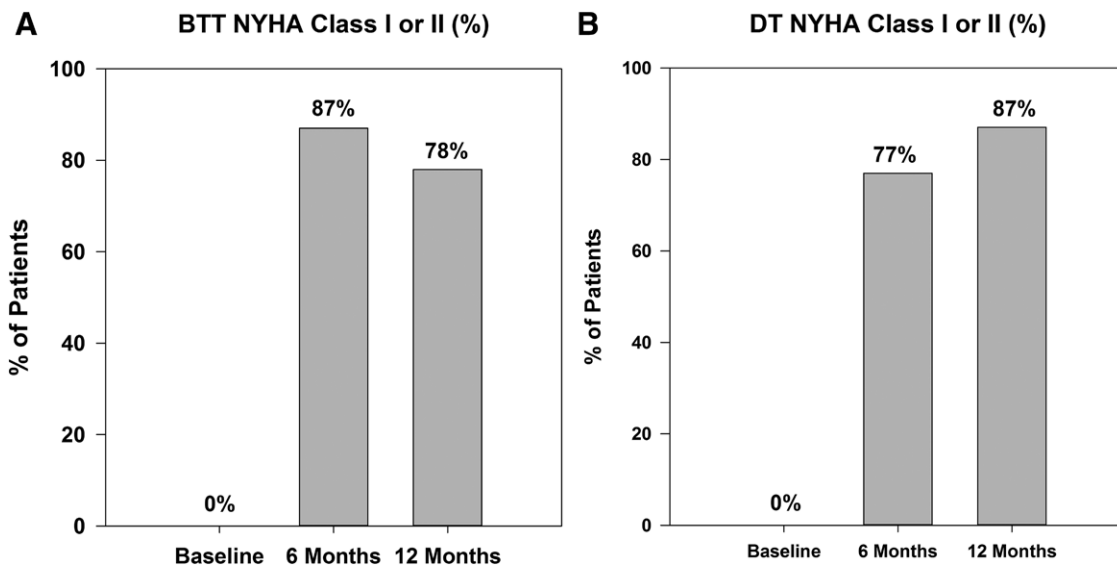


Figure 3. A: NYHA classification of BTT patients pre- and post-LVAD implant. **B:** NYHA classification of DT patients pre and post LVAD implant. BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device; NYHA, New York Heart Association.

Table 2. Baseline Characteristics: HMII BTT PAS Cohort

Characteristic	BTT (n = 169)
Age (year)	
<40	26 (15%)
40–59	81 (48%)
≥60	59 (35%)
Female sex (%)	38 (22%)
Race	
White	125 (74%)
Black	29 (17%)
Unknown/other	15 (9%)
INTERMACS profiles	
Profile 1	41 (24%)
Profile 2–3	96 (57%)
Profile 4–7	32 (19%)
Body surface area (m ²) (median ± SD)	2.03 ± 0.25

BTT, bridge to transplant; HMII, HeartMate II; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; PAS, post approval study.

1 year, respectively. Although not statistically significant, the small BSA DT cohort had improved 1 and 2 year post implant survival compared with the DT PAS (84% ± 6% vs. 74% ± 3% and 79% ± 8% vs. 61% ± 3%, respectively; $p = 0.105$).

The adverse event profile of the small BSA patients is equally as comparable with the post approval HMII BTT and DT studies (Tables 4 and 5). For the BTT population, the small BSA cohort had adverse event rates that were not statistically different from the HMII BTT PAS for all the major adverse events rates studied, with the exception that there was less bleeding noted in the small BSA cohort (0.91 vs. 1.44 eppy). Similarly, the adverse event profile for the DT population was not dissimilar from the post approval DT cohort, although more hemolysis was noted in the small BSA cohort (0.16 vs. 0.06 eppy). The reason for a higher incidence of hemolysis in the small BSA cohort is unclear. Increased hemolysis may be associated with the cannula position in a small BSA patient, smaller relative circulating blood volume passing through the rotor, or other factors all of which require further investigation. However it does not appear to be related to thrombus, which was similar at 0.03 to 0.04 eppy between cohorts, and stroke at 0.04 eppy was actually trending to be lower in the smaller patients but this did not reach statistical significance.

Table 3. Baseline Characteristics: HMII DT PAS Cohort

Characteristic	DT (n = 247)
Age (years)	
<40	6 (2%)
40–59	69 (28%)
≥60	172 (70%)
Female sex (%)	43 (17%)
Race	
White	185 (75%)
Black	45 (18%)
Unknown/other	17 (7%)
INTERMACS profiles	
Profile 1	18 (22%)
Profile 2–3	52 (64%)
Profile 4–7	10 (12%)
Ischemic etiology (%)	140 (57%)
NYHA class IV (%)	196 (79%)
Body surface area (m ²) (median ± SD)	2.01 ± 0.29
Weight (kg) (median ± SD)	85 ± 22

DT, destination therapy; HMII, HeartMate II; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association; PAS, post approval study.

Paralleling comparable post implant survival outcomes and adverse event profiles of the small BSA patients is the marked improvement in NYHA functional class with the majority of patients reporting class I/II post implant, suggesting that the small BSA patients enjoy not only morbidity and mortality benefits but also improved quality of life with LVAD therapy.

The US clinical trial of the HM II also studied two small BSA patient (BSA < 1.5) cohorts, one for DT (n = 24) and one for BTT (n = 10), which were analyzed separately in the trial. The BTT cohort was composed of 10 females and was published in the device labeling.⁶ All small BSA patients survived to 180 days post implant with 86% improving from NYHA class IV to class I/II after 3 months. Six minute walk distance also increased an average of 230 m in the small BSA cohort versus 247 m in the primary study cohort. Adverse event rates were similar to those measured in the primary study cohort. Patients with small body size were comparable with larger patients in the clinical study; however, the number of small BSA patients was too few to make definitive conclusions.

A recent report by Cabrera et al.⁸ utilizing the INTERMACS registry compared outcomes of 28 pediatric patients aged 11

Table 4. Adverse Events: BTT

	HMII Patients With a Small BSA (n = 82) (Total Duration: 107.9 Patient Years)		HMII BTT Post Approval Study (n = 169) (Total Duration: 142 Patient Years)		<i>p</i>
	% Patients	Events (Events/Patient Year)	% Patients	Events (Events/Patient Year)	
Bleeding	35 (43%)	98 (0.91)	75 (44%)	204 (1.44)	0.010
Explant due to device thrombosis	1 (1%)	1 (0.01)	NR	NR	NR
Hemolysis	5 (6%)	6 (0.06)	5 (3%)	5 (0.04)	0.458
Hepatic dysfunction	8 (10%)	8 (0.07)	11 (7%)	12 (0.08)	0.783
Any infection	33 (40%)	112 (1.04)	78 (46%)	142 (1.00)	0.836
Drive line infection	13 (16%)	30 (0.28)	30 (18%)	45 (0.32)	0.626
Pump pocket infection	1 (1%)	1 (0.01)	3 (1.8%)	3 (0.02)	0.467
Stroke	7 (9%)	7 (0.06)	11 (7%)	11 (0.08)	0.723
Renal dysfunction	11 (13%)	11 (0.10)	17 (10%)	19 (0.13)	0.496
Right heart failure	9 (11%)	12 (0.11)	25 (15%)	26 (0.18)	0.177

BSA, body surface area; BTT, bridge to transplant.

Table 5. Adverse Events: DT

	HMII Patients With a Small BSA (n = 46) (Total Duration: 55.9 Patient Years)		HMII DT Post Approval Study (n = 247) (Total Duration: 386 Patient Years)		p
	% Patients	Events (Events/Patient Year)	% Patients	Events (Events/Patient Year)	
Bleeding	29 (43%)	49 (0.88)	133 (54%)	324 (0.84)	0.836
Explant due to device thrombosis	2 (4%)	2 (0.04)	10 (4%)	12 (0.03)	0.857
Hemolysis	9 (20%)	9 (0.16)	16 (7%)	23 (0.06)	0.014
Hepatic dysfunction	4 (9%)	5 (0.09)	NR	NR	NR
Any infection	16 (35%)	47 (0.84)	NR	NR	NR
Drive line infection	6 (13%)	11 (0.20)	47 (19%)	85 (0.22)	0.749
Pump pocket infection	1 (2%)	1 (0.02)	NR	NR	NR
Stroke	2 (4%)	2 (0.04)	29 (12%)	32 (0.08)	0.245
Renal dysfunction	3 (7%)	3 (0.05)	44 (18%)	58 (0.15)	0.079
Right heart failure	5 (11%)	5 (0.09)	44 (18%)	62 (0.16)	0.223

BSA, body surface area; DT, destination therapy.

to 18 years compared with young adults aged 19 to 39 years implanted with the HMII. At 6 months, the composite of survival to transplantation, ongoing support, or recovery was 96% for the pediatric group, not dissimilar to the young adult group ($p = 0.330$). The median BSA for the pediatric group was 1.91 m² (1.47–2.65).

Interestingly, the results of the Japanese HMII prospective BTT trial were recently published.⁹ The six patients enrolled in this study had a mean BSA of 1.58 ± 0.17 m². All patients were inotrope dependent and failing medical management at baseline. Although a small trial, at 6 months post implant, there were no deaths and all patients were alive with ongoing support. Functional status assessed by the 6 minute walk distance increased from 268 ± 92 m at baseline to 399 ± 105 m, and 100% of the patients were reported to be NYHA class I/II in follow-up. All the six patients eventually were successfully transplanted.

Unlike previous studies, but similar to the small patient cohort in the US clinical trial, this report is unique in that the study population is predominantly female. The majority of clinical trials and investigations in heart failure have traditionally been comprised of predominantly male populations. In the mechanical circulatory support literature, the female sex is particularly underrepresented. This is especially true historically with the use of the first-generation pulsatile displacement pumps, where smaller anatomies were physically unable to accommodate the larger devices. A recent single center study looked at sex-specific outcomes in the CF-LVADs era.¹⁰ Their study population included 130 patients, 35 (27%) of whom were female. The investigators found comparable short and mid-term post implant survival outcomes, hospital length of stay, readmissions rates, and post operative complications between males and females.

Boyle et al.¹¹ retrospectively analyzed the pre operative risks for bleeding and stroke during CV-LVAD support in the HMII BTT and DT clinical trials. Of 956 patients, 220 (23%) were female. The authors found an increased incidence of thrombotic and hemorrhagic events in female patients compared with male patients. In this report, 83% of the study population was female, and with comparable post implant survival outcomes and adverse event rates matching the post approval LVAD studies, it may be suggested that females benefit as much from CF-LVAD therapy as their male counterparts.

Limitations

This study has several important limitations. The PASs included the small BSA cohort but because the majority of patients in the PAS had a BSA > 1.5 m², the impact of this inclusion would not be clinically significant. The BTT and DT PAS cohorts were not implanted during the same time-frame which may have influenced outcomes as management strategies are expected to improve with time and experience. The INTERMACS database was designed as a registry and not for the purpose of analyzing outcomes in small BSA patients implanted with CF-LVADs. Furthermore, the survival outcomes and adverse event rates of the small BSA patients compared with the post approval BTT and DT studies were not risk adjusted.

In conclusion, this study represents the largest cohort of adult patients analyzed with a small BSA < 1.5 m² receiving a CF-LVAD. The majority of the patient population was female. With comparable post implant survival outcomes and adverse event rates comparable with the published post approval BTT and DT studies, this study supports the use of CF-LVADs as BTT or DT in patients with a small BSA < 1.5 m².

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