HeartWare ventricular assist system for bridge to transplant: Combined results of the bridge to transplant and continued access protocol trial

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KEYWORDS: heart failure; quality of life; survival; ventricular assist device; continuous flow; bridge-to-transplant

BACKGROUND: The HeartWare Ventricular Assist System (HeartWare Inc, Framingham, MA) is a miniaturized implantable, centrifugal design, continuous-flow blood pump. The pivotal bridge to transplant and continued access protocols trials have enrolled patients with advanced heart failure in a bridge-to-transplant indication.

METHODS: The primary outcome, success, was defined as survival on the originally implanted device, transplant, or explant for ventricular recovery at 180 days. Secondary outcomes included an evaluation of survival, functional and quality of life outcomes, and adverse events.

RESULTS: A total of 332 patients in the pivotal bridge to transplant and continued access protocols trial have completed their 180-day primary end-point assessment. Survival in patients receiving the HeartWare pump was 91% at 180 days and 84% at 360 days. Quality of life scores improved significantly, and adverse event rates remain low.

CONCLUSIONS: The use of the HeartWare pump as a bridge to transplant continues to demonstrate a high 180-day survival rate despite a low rate of transplant. Adverse event rates are similar or better than those observed in historical bridge-to-transplant trials, despite longer exposure times due to longer survival and lower transplant rates. J Heart Lung Transplant 2013;32:675–683 © 2013 International Society for Heart and Lung Transplantation. All rights reserved.
year. In 2008, hospital costs related to heart failure exceeded U.S. $34 billion, and 1 in 8 death certificates mentioned heart failure. Overall, 50% of heart failure patients die within 4 years, and 40% of those hospitalized due to acute heart failure are readmitted or die within 1 year.

The gold standard for treatment of end-stage heart failure in suitable candidates is cardiac transplantation; however, donor availability is limited. Among candidates listed for transplant by United Network of Organ Sharing (UNOS) in 2010, the overall median waiting time was 6.6 months, with 12% waiting 5 years or more. However, the mortality rate on the waiting list has declined during the past 12 years, from 20.7% to 13.7%, due to improvements in care, including the use of mechanical support devices.

The use of ventricular assist systems as a bridge to transplantation (BTT) has increased in recent years due to design enhancements leading to improved device reliability, survival, functional capacity, and quality of life. In 2009, the number of patients that received mechanical circulatory support for BTT exceeded 30%. Recently updated European Society of Cardiology guidelines for treatment of acute heart failure added the use of left ventricular assist device (LVAD) or bi-VAD as a Class I/B recommendation in patients deteriorating on medical therapy while waiting for a heart transplant. The American Heart Association has also issued a guidance document describing the use of mechanical circulatory support for BTT as a Class I/B recommendation, as well as providing guidance in the referral of patients for VAD support.

The HeartWare Ventricular Assist System (HeartWare Inc, Framington, MA) is a miniaturized, implantable centrifugal design, continuous-flow blood pump. It uses a hybrid magnetic/hydrodynamic impeller suspension for novel frictionless rotation, and optimizes flow, pump surface washing, and hemocompatibility. The HeartWare VAD (HVAD) pump is connected to lightweight patient peripherals (controller, batteries) by a thin (4.2-mm), flexible driveline with fatigue-resistant cables. Compared with contemporary marketed VAD pumps, the HVAD has an integrated inflow cannula, allowing implantation within the pericardial space, and requires no abdominal surgery for formation of a pump pocket. The pump controller permits accurate flow estimation and maintains log files to enable flow and power waveform analyses.

In results from the pivotal Conformité Européenne Mark trial published by Strueber et al., the survival rates during support were 90%, 84%, and 79% at 6, 12, and 24 months, respectively, and significantly improved measures of quality of life over baseline were noted. The pivotal ADVANCE Clinical Trial was a multicenter clinical trial to evaluate the HeartWare HVAD System for BTT in patients with advanced heart failure in the United States. The HVAD pump was implanted in 140 patients who were compared with a prospective control group of 499 patients from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry who received a commercially available LVAD as a BTT. Survival in the BTT trial was 94% at 180 days and greater than 86% at 1 year, and functional capacity and quality of life improved markedly, with a favorable adverse event profile. After completion of enrollment of the BTT Trial and submission to the U.S. Food and Drug Administration (FDA), an additional 256 patients were enrolled to receive an HVAD as BTT under a continued access protocol (CAP). We report here the analysis of primary and secondary end points of combined data from the 140 BTT patients plus 192 patients from CAP who were monitored to outcome or who completed at least 6 months of follow-up.

Materials and methods

The study design of the HVAD BTT Clinical Trial was described previously. Briefly, the BTT Trial was a prospective, multicenter clinical trial to evaluate the HVAD as BTT in the United States. The trial enrolled 140 patients with advanced heart failure beginning in August 2008 who were eligible for heart transplantation at each center and were believed to be unable to survive without mechanical circulatory support. Detailed inclusion and exclusion criteria are provided in Table 1. These patients were compared with a contemporaneous control group of patients enrolled in INTERMACS who received a commercially available LVAD as a BTT. Patients were monitored for >180 days after implant or until cardiac transplantation, device explant for recovery, or death. The study met its primary end point, survival to 180 days on original device or transplant, demonstrating non-inferiority to the INTERMACS control, 92% vs 88% (non-inferiority p < 0.0001). The study is ongoing, as patients will be monitored through 5 years.

The FDA approved a continued access protocol (CAP) for the BTT indication for the 30 BTT clinical sites that enrolled at least 1 patient in BTT. The same enrollment criteria were in effect for the CAP as for BTT. The FDA granted 4 allotments of 54, 54, 94, and 54 additional patients under the CAP for a total of 256 patients. We present here data on the 140 patients enrolled in the ADVANCE BTT trial and an additional 192 patients enrolled under the CAP who were monitored to outcome or had completed 180 days of follow-up at the time of this analysis, July 31, 2012. The studies were conducted in compliance with FDA regulations for Good Clinical Practice, and were approved by each site’s Institutional Review Board. All patients or their authorized representatives provided informed consent.

Statistical analysis

Descriptive statistics were used to evaluate baseline demographics, incidence rates, and changes from baseline. Continuous data are expressed as mean ± standard deviation. Survival is reported descriptively through Kaplan-Meier analysis, with follow-up censored at the time of heart transplantation, device explant for recovery, withdrawal of consent, or loss to follow-up. Overall survival was defined as freedom from death from any cause, with censoring at the time of heart transplant or explant for recovery. Monitoring for an outcome event continued in any patient explanted for device exchange. Competing outcomes were calculated by Kaplan-Meier nonparametric product limit actuarial method.

Secondary end points included in this analysis were the incidence of all device failures and malfunctions, change in quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary score and the EuroQOL-5D Visual Analog Scale (EQ-5D VAS), and change in functional status as measured by the 6-minute walk test (6MWT). Values of 0 were imputed for patients unable to complete the 6MWT for any reason other than an incomplete follow-up visit.
### Table 1  BTT + CAP Study Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>1. Must be at least 18 years of age at enrollment.</td>
<td>1. Any ongoing mechanical circulatory support other than an intra-aortic balloon pump.</td>
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<td>2. Body surface area ≥1.2 m².</td>
<td>2. Prior cardiac transplant.</td>
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<td>3. Patient is New York Heart Association class IV.</td>
<td>3. History of confirmed, untreated abdominal or thoracic aortic aneurysm &gt; 5 cm.</td>
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<td>4. Patient listed for cardiac transplantation.</td>
<td>4. Cardiothoracic surgery within 30 days of enrollment.</td>
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<td>5. Patient meets United Network for Organ Sharing Status 1A or 18 listing criteria.</td>
<td>5. Acute myocardial infarction within 14 days of implant as diagnosed by ST or T wave changes on the electrocardiogram, diagnostic biomarkers, ongoing pain, and hemodynamic abnormalities, as described in published guidelines.4</td>
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<td>6. HVAD implant is planned as a bridge to transplant.</td>
<td>6. On ventilator support for &gt;72 hours within the 4 days immediately before enrollment.</td>
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<td>7. The patient or legally authorized representative has signed the informed consent form.</td>
<td>7. Pulmonary embolus within 3 weeks of enrollment as documented by computed tomography scan or nuclear scan.</td>
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<td>8. Symptoms of cerebrovascular disease or a &gt; 80% carotid stenosis.</td>
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<td>10. Patients with mechanical, animal, or human tissue heart valves.</td>
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<td>11. Severe right ventricular (RV) failure as defined by the anticipated need for RV assist device support or extracorporeal membrane oxygenation at the time of HVAD screening/enrollment or right atrial pressure &gt; 20 mm Hg on multiple inotropes, RV ejection fraction &lt; 15%, or clinical signs, including lower extremity edema, ascites or pleural effusions refractory to treatment with diuretics and 2 inotropic drugs.</td>
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<td>12. Active, uncontrolled infection diagnosed by a combination of clinical symptoms and laboratory testing, including but not limited to, continued positive cultures, elevated temperature and white blood cell count, hypotension, tachycardia, generalized malaise despite appropriate anti-biotic, anti-viral, or anti-fungal treatment.</td>
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<td>13. Uncorrected thrombocytopenia or generalized coagulopathy (eg, platelet count &lt; 100,000, INR &gt; 1.6, or PTt &gt; 2.5 times control in the absence of anticoagulation therapy).</td>
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</tr>
<tr>
<td>14. Intolerance to anti-coagulant or anti-platelet therapies or any other peri-operative or post-operative therapy that the investigator may administer based on the patient’s health status.</td>
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<td>15. Serum creatinine &gt; 3.0 times the upper limit of normal within 48 hours of study enrollment or requiring dialysis (does not include use of ultra-filtration for fluid removal).</td>
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All adverse events, including those meeting the INTERMACS definitions (www.uab.edu/intermacs/appendices/appendix-a), were evaluated with respect to classification and device-relatedness. Adverse event and device failures were reported as the percentage of participants affected and the rate of events per patient-year (EPPY) of follow-up. Kaplan-Meier estimates of the probability of device failures or malfunctions were also obtained. Descriptive statistics were provided for the other secondary end points and safety measures.

In patients receiving warfarin, the method of Rosendaal et al11 was used to calculate the overall time that international normalized ratio (INR) values fell within the therapeutic range.

### Results

#### Baseline characteristics

Between August 2008 and December 2011, 332 patients (71% men) were enrolled at 30 centers in the United
States. Baseline demographics are described in Table 2. Patients were a mean age of 52.8 ± 11.9 years, and the mean body surface area was 2.0 ± 0.3 m². Heart failure due to ischemic heart disease was present in 36.7%, and 58.4% had a history of hypertension. The mean left ventricular ejection fraction was 17.4 ± 7.4%, and the mean cardiac index was 2.1 ± 0.6 liters/min/m². New York Heart Association Functional Class IV heart failure classification was recorded for 95.5% of patients. INTERMACS 4 to 7 classification was reported for 18% of patients, 42% were INTERMACS 3, 35% were INTERMACS 2, and 5.4% were INTERMACS 1.

**Outcomes**

Patients were monitored for at least 180 days or until transplant or death. Kaplan-Meier survival analysis for the

![Image](image-url)

**Figure 1** Survival analysis for combined HVAD bridge to transplant (BTT) and continuous access protocols (CAP; n = 332).
combined BTT and CAP patients revealed survival at 60, 180, and 360 days was 97%, 91%, and 84%, respectively (Figure 1). Competing outcomes methodology showed 67.1% of patients were alive on the originally implanted study device at 180 days, and 21.4% had received a transplant or the device was explanted for recovery during this 6-month post-implant period (Figure 2). Death ≤180 days occurred in 6.9% of patients. Survival of patients who received a transplant or whose device was explanted for recovery after support on the HVAD was 90% at 180 days and 89% at 360 days after transplant or explant.

A review of patient status through July 2012 revealed that of the 140 patients originally enrolled in the HVAD BTT Trial, 37 (26.4%) remained on support for greater than 2 years, some of whom eventually received a transplant, and 7 of these remained on support for more than 3 years. There were 55 deaths while on a mechanical support device among 332 patients in the combined cohorts, including 8 who were exchanged from the initial device for multiple reasons.

The most common causes of death were neurologic events and multisystem organ failure, each occurring in 24% of patients who died. Other less frequent causes of death, by decreasing frequency, included cardiopulmonary failure (9%), infection or pneumonia (7%), right heart failure (5%), and hemorrhage, respiratory failure, and controller malfunction (4% each). Cardiac arrhythmia, hepatic failure and ischemic bowel complications led to death in less than 6% of patients. The cause of death was unknown in 13% of patients.

A total of 63% of patients completed paired functional capacity measurements (6MWT) at baseline (pre-implant) and at 180 days after implant. In addition, 51% of patients completed paired KCCQ, and 54% completed paired EQ-5D VAS quality of life measurements. Of 224 patients who were available for follow-up at 6 months (ie, no transplant, device explant for recovery, or dead, and had reached the 6 month post-implant assessment), paired data were obtained on 209 for the 6 MWT, 178 for the EQ-5D VAS, and 169 for the KCCQ. Of patients completing the paired 6MWT assessments, there was a statistically significant improvement of 185.4 meters (Figure 3). The EQ-5D VAS and KCCQ Overall Summary scores showed statistically significant improvements of 27.4 and 30.9 points, respectively. Overall, there was a statistically significant improvement of 38% in the EQ-5D VAS and 46% in the KCCQ scores from baseline to 6 months (Table 3).

Adverse events

Adverse event rates compared favorably with historical rates with LVADs as BTT (Table 4). Follow-up time ranged from 6 to just over 36 months for patients alive on the original device. Driveline exit site infections occurred in 56 patients (16.9%), at an event rate of 0.25 EPPY, and sepsis occurred in 57 (17.2%) at 0.23 EPPY. Freedom from driveline infections and sepsis was 89% and 90% at 180 days and 83% and 80% at 1 year, respectively (Figure 4A). Bleeding requiring reoperation occurred in 49 (14.8%) at a rate of 0.19 EPPY. Gastrointestinal bleeding was identified in 42
patients (12.7%), and freedom from gastrointestinal bleeding was 91% at 180 days and 86% at 1 year (Figure 4B). Cardiac tamponade was reported in 17 patients (5.1%) and cardiac arrhythmias in 120 (36.1%) with 20 patients having multiple events. Supraventricular tachycardias were more common in the perioperative period (0–30 days). Right heart failure occurred in 96 patients (28.9%), who were mostly treated with inotropic therapy. RVAD use was rarely required (3.3%).

A stroke event occurred in 14.8% (2 patients having both ICVA an HCVA) of patients, and overall, 28.6% of stroke events were fatal. Ischemic cerebrovascular accidents (ICVA) occurred in 7.5% of patients, at a rate of 0.09 EPPY, and hemorrhagic CVA (HCVA) occurred in 7.8%, at a rate of 0.09 EPPY, and 46% were fatal. With respect to timing of events, 61% of ICVAs occurred after discharge, at a rate of 0.06 EPPY, and 75% of HCVAs occurred after discharge at a rate of 0.08 EPPY. Furthermore, 65% of ICVA patients had a Modified Rankin score (MRS) of 2 or less, 25% had no residual neurologic deficit (MRS, 0), and 22 of 25 patients (88%) with ICVAs survived their event.

**Effect of medical therapy and device design enhancements**

In March 2011, HeartWare reviewed anticoagulation therapy, strokes, VAD thrombus, and gastrointestinal bleeding. At that
time, device exchanges occurred at a rate of 0.07 EPPY. Specifically, procedure-related device exchanges occurred at a rate of 0.01 PPY, whereas suspected thrombus-related device exchange occurred at 0.063 PPY. Most patients with VAD thrombus (1) had sub-therapeutic INRs and (2) were taking 81 mg aspirin or no acetylsalicylic acid (ASA). Moreover, the rates of bleeding or hemorrhagic strokes in patients with therapeutic INR combined with ASA at 325 mg/day were not higher than those patients who were at sub-therapeutic levels. Hence, the Principal Investigators recommended in March 2011 that strict adherence to the protocol INR requirement of 2.0 to 3.0 be followed and that the ASA dose be advanced to 325 mg. After March 15, 2011, and through July 30, 2012, the use of the higher dose of ASA (162–325 mg) rose from 54% to 67%. A shift also occurred in the median time in therapeutic INR range (2.0–3.0) from 35% to 46%. The annualized rate of pump exchange for suspected thrombus dropped from 0.063 to 0.027, a level 55% less than the rate before the anticoagulation adjustment (Figure 5).

During the same interval (after March 15, 2011, through July 30, 2012), the incidence of ischemic strokes resulting in any disability (MRS > 0) declined as well (Table 5). The incidence of ischemic strokes resulting in any level of neurologic disability declined from 5.1% (0.089 EPPY) to 2.8% (0.047 EPPY). The incidence of hemorrhagic strokes resulting in any level of neurologic disability was relatively unchanged, from 5.1% (0.082 EPPY) to 4.7% (0.074 EPPY).

**Discussion**

These data continue to support the findings from the HVAD BTT pivotal trial regarding the safety and efficacy of the HVAD pump in patients with end-stage heart failure requiring an LVAD as a BTT. Overall survival remains high, at 91% at 180 days and 84% at 1 year, despite lower transplant rates than in prior BTT trials. Survival also compares favorably or better than survival rates published with other commercially available VADs for BTT, including survival after transplant. Patients with advanced heart failure experience significant impairment in quality of life and functional capacity. Improved survival and longer waiting times for transplant after LVAD implantation means quality of life and functional capacity outcomes are especially important. Quality of life and functional capacity were substantially improved at 6 months in recipients of the HVAD. The distance walked in the 6MWT more than tripled, and statistically significant improvements of 84% and 62% were observed in the KCCQ and in the EQ-5D VAS scores from baseline to 6 months, respectively. These functional and quality of life improvements are similar to those reported in the HeartMate II (Thoratec, Pleasanton, CA) BTT Trial.

Adverse event rates remain low and are similar to those published with the currently approved device, the HeartMate

| Event | Overall BTT + CAP (N = 332) | Patients with event | | | |
|-------|-----------------------------|---------------------|---------------------|---------------------|
|       |                             | <03/15/2011<sup>a</sup> | EPPY | >03/15/2011<sup>a</sup> | EPPY |
|       | % (n) | (158.18 years) | % (n) | (147.68 years) |  |
| All ICVAs | 6.3 (16/253) | 0.107 | 4.7 (10/211) | 0.074 |
| ICVAs with MRS > 0<sup>b</sup> | 5.1 (13/253) | 0.089 | 2.8 (6/211) | 0.047 |
| All HCVAs | 5.1 (13/253) | 0.082 | 6.6 (14/211) | 0.102 |
| HCVAs with MRS > 0<sup>b</sup> | 5.1 (13/253) | 0.082 | 4.7 (10/211) | 0.074 |

BTT, bridge to transplant; CAP, continued access protocols; EPPY, events per patient-year; HCVA, hemorrhagic cerebrovascular accident; ICVA, ischemic cerebrovascular accident; MRS, Modified Rankin score.

<sup>a</sup>Patients whose follow-up crossed the time periods were included in both denominators.

<sup>b</sup>Determined at 4 to 8 weeks after stroke.
of bleeding was observed at a rate of 0.27 EPPY. The overall rate of only 0.19 EPPY each, whereas gastrointestinal events were very low compared with published rates, occurring at an overall rate of only 0.05 EPPY. Later in the CAP trial, Pagani et al reported an ICVA occurred in 6% of (0.13 EPPY) and an HCVA in 2% (0.05 EPPY). In the CAP trial, Pagani et al. reported ICVAs in 5% of patients (0.09 EPPY) and HCVAs in 3% (0.05 EPPY). The fatality rate of all strokes occurring in the HeartMate II CAP trial was 40% (10 of 25), whereas the fatality rate after an HCVA was 56% (5 of 9). We observed an overall stroke fatality rate of only 28.6% in the BTT and CAP trials using the HVAD and a 46% mortality rate after an HCVA. Furthermore, 25% of patients with an ICVA fully recovered, with no residual neurological deficits (MRS, 0) and 88% (22 of 25) survived their event.

A review of the anti-coagulation and anti-platelet medication data during CAP enrollment prompted recommendation of an adjustment of the daily aspirin dose from 81 to 325 mg and a request to target the maintenance INR range to 2.0 to 3.0. Pump exchange rates for suspected pump thrombus decreased by 55% to very low levels after this change in recommended anti-coagulation and aspirin therapy (Figure 5). Moreover, ischemic strokes with any level of disability (MRS >0) declined from 5.1% (0.089 EPPY) to 2.8% (0.047 EPPY; Table 5). Aspirin and anti-coagulation therapy use with the HVAD was without an increased risk of bleeding complications.

Our data thus indicate that patients receiving a HVAD as a BTT have excellent 6-month and 1-year survival, significant improvements in quality of life, and adverse event rates comparable to or lower than those reported in comparable clinical trials, including a very low exchange rate for VAD thrombus. In the course of the study, a reduction in the incidence of strokes and device exchanges due to suspected thrombus was observed after adjustments in clinical anti-coagulation management.

This study has several limitations. First, this was not a randomized trial; all patients received the HVAD. However, at the time of initiation of the HVAD BTT trial, the HeartMate II was not yet approved, and clinicians were reluctant to implant the FDA-approved XVE device due to its relatively large size, poor durability, and adverse event profile. HeartWare and FDA determined that using a sufficiently large subset of INTERMACS patients would be an appropriate comparator to the HVAD treatment arm.

Another limitation is that adverse event rates can only be compared with historical literature. However, the contemporary control from the INTERMACS database was limited in its availability of reported adverse event rates. The reference data sets in publications from controlled studies of the HeartMate II in the BTT population supports the hypothesis that the HVAD is at least as safe as the commercially available LVADs.

In conclusion, the ongoing data from the CAP cohort of the HVAD BTT trial continue to support the overall survival, significantly improved quality of life, and overall safety and reliability of the HVAD system in patients with end-stage heart failure requiring a BTT. Rates of bleeding, infections and device exchanges due to thrombus were very low, and the survival of patients going on to cardiac transplantation was excellent. Ongoing patient management strategies have decreased the incidence of device exchanges and disabling strokes, and continue to result in improved patient outcomes in this population.

**Disclosure statement**

This study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) with the Unique Identifier NCT00751972.

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