Low Operative Mortality With Implantation of a Continuous-Flow Left Ventricular Assist Device and Impact of Concurrent Cardiac Procedures

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Background—The objective of this study was to determine the impact of concurrent cardiac procedures (CCP) on patient outcomes after HeartMate II (HMII) left ventricular assist device implantation.

Methods and Results—Two hundred eighty-one patients underwent implantation of a HMII as a bridge to transplantation from March 2005 to March 2007. One hundred seventy patients had an HMII implanted only, and 81 patients underwent concurrent cardiac procedures in conjunction with HMII implantation (HMII/CCP). Of these, 47 patients had concurrent valvular procedures, 15 patients had simultaneous closure of patent foramen ovale, and 19 patients had other various cardiac procedures. Patients requiring right ventricular assist device support or noncardiac procedures were excluded. Preoperative characteristics were similar for patients with and without concurrent cardiac procedures. Overall 30-day mortality was 5.8% for the HMII group and 11.3% for the HMII/CCP group. Subgroup analysis demonstrated that simultaneous patent foramen ovale closure was not associated with an increased 30-day mortality rate, but concurrent valvular procedures increased the risk to 8.5%. Patients who underwent an aortic valve procedure had a 30-day mortality rate of 25%, higher than for isolated concurrent mitral (0%) or tricuspid repair (3.3%). Survival at 180 days was 87% for HMII alone and 80% for HMII/CCP. The hazard ratio for concurrent cardiac procedures adjusted for baseline parameters was 1.82 (95% CI, 1.07 to 3.10, P=0.026).

Conclusions—There is a low 5.8% operative mortality rate for patients requiring uncomplicated HMII implantation, with no apparent increased risk for concurrent patent foramen ovale closure or mitral or tricuspid repair. However, concurrent aortic valve and other cardiac procedures are associated with significantly decreased perioperative and long-term survival. (Circulation. 2009;120[suppl 1]:S215–S219.)

Key Words: left ventricular assist device ■ transplantation ■ mechanical circulatory support

Implantable left ventricular assist device (LVAD) technology has progressed from first-generation pulsatile designs to continuous-flow pumps using axial flow and centrifugal designs. These changes have resulted in greater durability and smaller size. The HeartMate II (HMII) axial-flow pump is approximately 20% of the size of the earlier HeartMate XVE pulsatile LVAD.1–5 This new device technology has enabled easier and shorter implant procedures. In this report, we review early results with the HMII pump used as a bridge to transplant. The cohort presented consists of all patients enrolled in the HeartMate II Bridge to Transplant (HMII BTT) trial, a multicenter, clinical study that led to Food and Drug Administration approval in April 2008 for the indication of bridge to transplantation.

LVAD implant procedures may involve concomitant procedures to help address cardiac lesions not directly corrected by the mechanical replacement of the left ventricle.1 For example, patients with atrial septal defects often undergo repair to prevent right-to-left shunting of deoxygenated blood, which would accompany left heart unloading. Similarly, experts have recommended additional procedures for significant aortic insufficiency to prevent recirculation of pump output through the incompetent valve.6–8 Other procedures, such as repair of regurgitant mitral or tricuspid valves, have been advocated by some to further improve hemodynamic outcomes. However, although a variety of concurrent cardiac procedures have been described, the additive procedural risk is poorly defined. In addition, the long-term benefits of concurrent procedures with LVAD implantation are unknown. In an effort to begin to examine the risk-benefit relationship for such concurrent procedures, we review outcomes from the HMII BTT trial, examining specifically the
cohort of patients who underwent HMII LVAD implantation and also had concurrent cardiac procedures versus patients who had isolated LVAD implantation.

Most of the concurrent procedures performed in the HMII BTT trial are relatively simple cardiac surgical procedures that have been extensively characterized. However, the application of these procedures to a highly decompensated heart failure population at the time of LVAD implantation has not been previously examined. These patients have some degree of secondary end-organ dysfunction that usually is not present with conventional cardiac procedures. This compromised preoperative state may increase the risk of these combined procedures. Importantly, some of these procedures are geared toward supporting right heart performance, which is a limitation to early outcomes with implantable LVADs9–10, an important example of this would be tricuspid valve repair or replacement for tricuspid insufficiency. Unfortunately, increased cardiopulmonary bypass time or cardiopлегic arrest required for these procedures could lead to more coagulopathy and bleeding, which would negatively impact right ventricular performance. Therefore, decision-making regarding these procedures is complex, and analysis of additive risk in a larger study with well-defined outcomes is valuable.

Methods

The HMII BTT study was conducted at 33 clinical sites from March 2005 until March 2007 and supervised by the Food and Drug Administration and Thoratec Corporation. The initial bridge to transplant study included 133 patients enrolled at 26 sites.1 An additional 148 patients were enrolled in a continued access protocol, for a total of 281 patients who were included in this analysis.2

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Methods

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Patients listed for heart transplantation at the study centers were eligible for enrollment. Further inclusion criteria were United Network of Organ Sharing (UNOS) 1A or 1B status with impaired hemodynamics (pulmonary capillary wedge pressure >20 mm Hg; cardiac index, <2.2 L/min/m²; or systolic blood pressure ≤90 mm Hg). Patients were excluded for study participation if they had any mechanical circulatory support other than an intra-aortic balloon pump, body mass index >40 kg/m², or history of cardiac transplantation. In addition, patients were excluded by the presence of severe end-organ dysfunction manifested by international normalized ratio ≥2.5 not on anticoagulation therapy, bilirubin >5 mg/dL, cirrhosis, severe chronic obstructive pulmonary disease or restrictive lung disease, fixed pulmonary hypertension (pulmonary vascular resistance >6 Wood units), unresolved stroke, creatinine ≥3.5, or dialysis. Notably, patients with severe aortic insufficiency were required to undergo concurrent valve repair or replacement to be included in this trial. All patients provided written informed consent. Further inclusion and exclusion criteria have been previously reported.3

Baseline demographic and hemodynamic data were collected on all patients at time of enrollment. After device implantation, a standardized anticoagulation regimen was implemented. Postoperative care was according to the individual investigator’s preference and practice.

Of the 281 bridge to transplant patients who underwent implantation of a HMII pump, 111 had additional procedures performed at the time of the initial operation. Of these, 14 were noncardiac procedures and 97 were concurrent cardiac procedures. We excluded an additional 16 patients who underwent placement of a right ventricular assist device because this was generally not planned and signified a failure of LVAD therapy by itself to support the patient’s circulation. Therefore, we compared 170 patients who underwent isolated HMII implantation with 81 patients with HMII implantation with concurrent cardiac procedures (Figure 1).

The primary study outcomes examined for this report were mortality at 30 days after the procedure and survival to transplantation, recovery of ventricular function, or ongoing support at 180 days. Causes of mortality and frequency of adverse events were recorded for all patients. Definitions of adverse events were as previously published.2

Differences in continuous variables between patient groups were evaluated with an independent-samples t test and categorical variables with a Fisher exact test. Actuarial survival analysis was performed by the Kaplan–Meier method with censoring of patients for heart transplantation or ventricular recovery. Differences in survival were performed with a log-rank test. Cox proportional hazards analysis was used to estimate the relative risk ratios (with 95% CIs) for concurrent procedures adjusted for differences in baseline parameters. All baseline parameters were input into the model, and those with a probability value of <0.05 were retained as covariates. The level of statistical significance was set at a probability value of <0.05.

Results

Demographic, laboratory, and hemodynamic data for patients who underwent isolated LVAD placement are compared with those who had a concurrent cardiac procedure in Table 1. Most patients were male with an average age of 50 years. No significant difference existed in age, sex, renal or hepatic function, etiology, or the incidence of mechanical ventilation. Preoperative central venous pressures were higher in the group who underwent a concomitant cardiac procedure (14.5 ±6.9 mm Hg versus 11.6±6.1 mm Hg, P=0.001). A list of concurrent procedures in the 81 HMII patients is shown in Table 2. Forty-seven patients had a concurrent valvular

Table 1. Baseline Characteristics for Patients With HMII Implantation Alone and Those With Implantation and Concurrent Cardiac Procedures

<table>
<thead>
<tr>
<th></th>
<th>HMII</th>
<th>HeartMate II + CCP</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (n=170)</td>
<td>51±13</td>
<td>50±14</td>
<td>0.578</td>
</tr>
<tr>
<td>Female, % (n=170)</td>
<td>25.9</td>
<td>18.5</td>
<td>0.265</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.4±0.5</td>
<td>1.5±0.6</td>
<td>0.167</td>
</tr>
<tr>
<td>CVP (mm/Hg)</td>
<td>11.6±6.1</td>
<td>14.5±6.9</td>
<td>0.001</td>
</tr>
<tr>
<td>INR</td>
<td>1.30±0.34</td>
<td>1.34±0.33</td>
<td>0.380</td>
</tr>
<tr>
<td>Ischemic, % (n=81)</td>
<td>41.8</td>
<td>39.5</td>
<td>0.785</td>
</tr>
<tr>
<td>Mechanical ventilation, %</td>
<td>5.9</td>
<td>8.6</td>
<td>0.429</td>
</tr>
</tbody>
</table>

CCP indicates concurrent cardiac procedures; CVP, central venous pressure; INR, international normalized ratio.
HMII II Implantation Alone or With Concurrent Cardiac Procedures

Table 3. Cardiopulmonary Bypass Time and Length of Stay for HMII II Implantation alone or with concurrent cardiac procedures was 121 minutes, significantly greater than for isolated LVAD placement (100±37 minutes) (Table 3). Median length of stay from date of device explantation. Differences in overall survival rates were statistically significant between the 2 groups (P=0.048, log rank test). The hazard ratio for concurrent procedures adjusted for baseline parameters was 1.82 (95% CI, 1.07 to 3.10; P = 0.026).

Subgroup analysis was performed to identify patients at higher risk for death after concurrent cardiac procedures (Table 4). Patients who underwent closure of a patent foramen ovale (PFO) at the time of LVAD placement were at no additional risk, as exemplified by 30-day mortality rate of 0%. The group of patients with concomitant valvular procedures had an overall operative mortality rate of 8.5%. Within this group, the 30-day mortality rate for tricuspid valve procedures (n=30) was 3.3% and 0% for mitral valve procedures (n=5). Aortic valve procedures (n=12), however, had an increased 30-day mortality rate of 25%.

There were no significant differences for the incidence of adverse events (Table 5) or causes of death (Table 6) for patients with isolated HMII implantation and those who underwent implantation with concurrent cardiac procedures. Details of the causes of death for the 2 subgroups with the highest mortality rate demonstrated that 3 of the 12 patients

Table 2. Concurrent Cardiac Procedures (n=81)

Valvular procedures (n=47)
  Tricuspid (n=30)
  Aortic (n=12: 8 aortic valve replacement, 4 valve patch)
  Mitral (n=5)
PFO closure (n=15)
Removal of LV thrombus (n=3)
LV aneurysm resection (n=3)
Insert ICD/Repair ICD lead (n=3)
CABG (n=2)
LV laceration repair (n=2)
RV ablation
VSD repair
RA thrombectomy
Repair of dissection of ascending aorta
LV remodeling
Lysis of intrapericardial adhesions

CABG indicates coronary artery bypass grafting; RV, right ventricular; VSD, ventricular septal defect; RA, right atrial.

Cardiopulmonary bypass times for patients with LVAD implantation plus concurrent cardiac procedures was 121±40 minutes, significantly greater than for isolated LVAD placement (100±37 minutes) (Table 3). Median length of stay from date of device implantation was 4 days longer (26.5 days) for patients with concurrent cardiac procedures compared with patients with isolated HMII implantation (23 days).

The 30-day mortality rate for patients with isolated HMII implantation was 5.9% compared with 11.1% for patients with concurrent procedures. In addition, survival to transplantation, recovery of ventricular function, or ongoing device support at 180 days was 87% for HMII alone versus 80% for HMII plus concurrent cardiac procedures (Table 4). Overall actuarial survival for patients receiving LVAD implantation with and without concurrent cardiac procedures is depicted in Figure 2. One-year survival was 77±4% for isolated HMII implantation and 66±7% for patients also requiring concurrent cardiac procedures. Patients recovering ventricular function or undergoing heart transplantation were censored at time of device explantation. Differences in overall survival rates were statistically significant between the 2 groups (P=0.048, log rank test). The hazard ratio for concurrent procedures adjusted for baseline parameters was 1.82 (95% CI, 1.07 to 3.10; P = 0.026).

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Table 3. Cardiopulmonary Bypass Time and Length of Stay for HMII II Implantation Alone or With Concurrent Cardiac Procedures

<table>
<thead>
<tr>
<th></th>
<th>HMII (n=170)</th>
<th>HMII+CCP (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary bypass times, min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>100±37</td>
<td>121±40*</td>
</tr>
<tr>
<td>Median</td>
<td>98.5</td>
<td>123.5</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>30±24</td>
<td>35±27</td>
</tr>
<tr>
<td>Median</td>
<td>23</td>
<td>26.5</td>
</tr>
</tbody>
</table>

*P<0.001.

CCP indicates concurrent cardiac procedures.
who had concomitant aortic valve procedures died within 30 days of the procedure: 1 with a patch procedure died of sepsis on postoperative day (POD) 5, whereas the 2 other patients with aortic valve replacements died on POD 7 with ischemic stroke and POD 18 with complications of right ventricular failure, respectively. Two additional patients with HMII plus aortic valve replacement died between 30 and 180 days, 1 of sepsis on day 133 and 1 of an undetermined cause on day 59.

Five of 19 patients who underwent implantation of the HMII plus other miscellaneous cardiac procedures died within 30 days; the causes of death are the following: 1 patient with left ventricular remodeling plus redo mitral valve repair and tricuspid valve anuloplasty died on POD 6 of complications of a malpositioned LVAD inflow graft, 1 patient with concomitant radiofrequency ablation and peritoneal dialysis catheter insertion died on POD 10 of sepsis, and 1 with repair of a dissection of the ascending aorta and Alfieri-type repair of the mitral valve died on day 20 of delayed postoperative hemorrhage. A patient with a left ventricular aneurysm resection and mitral valvuloplasty died on POD 26 of complications of right heart failure, and 1 patient with concurrent defibrillator placement died of an ischemic stroke on day 30. There were no other deaths within 180 days in this subgroup.

### Discussion

This study confirms encouraging outcomes with the HMII left ventricular assist system.\(^1\)\(^-\)\(^5\)\(^,\)\(^12\)\(^,\)\(^14\) Isolated implantation of the device without any additional procedures carried an operative (30-day) mortality rate of 5.9%, which is similar to outcomes from other types of conventional heart surgery for advanced heart failure. For example, LVAD implantation in this review has a procedural risk similar to that of heart transplantation (3%) and left ventricular aneurysmectomy (7.2%), based on recent Society of Thoracic Surgeons data.\(^13\) The smaller design relative to first-generation devices probably contributes to the favorable outcomes. In addition, as previously shown, pump performance enabled rapid restoration of hemodynamics and functional recovery, which probably also positively affected recovery from the procedure.\(^1\)\(^,\)\(^14\) Finally, well-defined inclusion and exclusion criteria for the HMII BTT trial avoided patients with advanced end-organ dysfunction who have been previously shown to have the greatest procedural mortality.\(^15\)

The results from HMII implants compare favorably with previous implantable LVAD studies. For example, the BTT trial avoided patients with advanced end-organ dysfunction who have been previously shown to have the greatest procedural mortality.\(^15\)

A small group of implants with concurrent mitral repair were identified. These repairs were all performed through the left ventricular apex without cardioplegic arrest. There were no deaths in this group, suggesting no additive risk. From a technical perspective, these cases were similar to tricuspid repair or closure of a PFO because they did not require the added complexity or risk of cardioplegic arrest.

### Table 5. Incidence of Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>HMII (n=170)</th>
<th>HMII + CCP (n=81)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>26%</td>
<td>25%</td>
<td>0.877</td>
</tr>
<tr>
<td>Sepsis</td>
<td>17%</td>
<td>18%</td>
<td>1.000</td>
</tr>
<tr>
<td>Driveline infection</td>
<td>10%</td>
<td>18%</td>
<td>0.132</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>20%</td>
<td>22%</td>
<td>0.743</td>
</tr>
<tr>
<td>Perioperative stroke</td>
<td>4%</td>
<td>2%</td>
<td>0.391</td>
</tr>
<tr>
<td>Renal failure</td>
<td>14%</td>
<td>8%</td>
<td>0.259</td>
</tr>
</tbody>
</table>

CCP indicates concurrent cardiac procedures.

### Table 6. Causes of Death

<table>
<thead>
<tr>
<th>Event</th>
<th>HMII (n=170)</th>
<th>HMII + CCP (n=81)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSOF</td>
<td>1.8%</td>
<td>1.2%</td>
<td>1.000</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.2%</td>
<td>3.7%</td>
<td>0.332</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.8%</td>
<td>1.2%</td>
<td>0.542</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>1.2%</td>
<td>2.5%</td>
<td>0.596</td>
</tr>
<tr>
<td>CVA</td>
<td>3.0%</td>
<td>4.9%</td>
<td>0.332</td>
</tr>
</tbody>
</table>

CVA indicates concurrent cardiac procedures; MSOF, multiple system organ failure; CVA, cerebrovascular accident.

a 30-day mortality rate of 19% and 1-year actuarial survival of 53% compared with the isolated HMII BTT mortality rate in this study of 5.9% and 77%, respectively.\(^16\) Even greater difference is seen comparing these results with those of Hernandez et al,\(^17\) in which a historical Medicare database was reviewed showing a 1-year survival rate of 51.6% for primary LVAD implantation. Improved outcomes with the newer HMII device probably are due to the advanced technology and also to implantation at select, more experienced centers relative to the Medicare review, which included mainly first-generation LVAD devices implanted at centers with varied experience.

Overall survival was better for the isolated HMII group versus the group with concurrent cardiac procedures. With regard to subgroups, there appeared to be no additive risk for closure of PFO and tricuspid procedures, which generally do not require cardioplegic arrest of the heart. These procedures generally require small periods of additional cardiopulmonary bypass support. Tricuspid procedures are generally used for patients with significant tricuspid insufficiency. Although left ventricular unloading may lead to gradual reduction of right ventricular afterload and subsequent reduction of tricuspid insufficiency, this process may occur over a period of months. Furthermore, tricuspid insufficiency may in some cases be acutely worse after implantation of an LVAD because of leftward shift of the intraventricular septum.\(^11\)\(^,\)\(^18\) For these reasons, surgical correction of tricuspid valve insufficiency with repair or replacement may provide early clinical benefits. The absence of additive procedural risk suggests that it is safe to address tricuspid insufficiency at the time of LVAD implantation. The increased late mortality associated with tricuspid procedures probably represents further right ventricular dysfunction rather than a complication of the concurrent procedure.
artery pressures. For these reasons, aortic valve regurgitation must be considered during LVAD implantation. However, the risk of concurrent procedures appeared greatest for the subset of patients undergoing aortic valve procedures. Specifically, this subgroup had a 30-day mortality rate of 25%, which was a nearly 5-fold increase relative to isolated HMII implants. Aortic valve procedures generally require cardiopulmonary arrest, which may have had a negative impact on right ventricular function, explaining some of the reduced outcomes. In addition, patients who undergo mechanical replacement have abnormal washing of the prosthesis, which may predispose to thrombus formation and embolic complications. Replaced valves may also seal in a closed position with endothelial overgrowth, resulting in loss of the native heart as a back-up system. Similarly, the operative strategy of completely overcoming the valve results in loss of the native heart back-up. Correcting aortic insufficiency during LVAD implantation is associated with higher operative mortality than previously described. Therefore, the decision to address aortic valve regurgitation must consider the additional procedural risk balanced against the potential hemodynamic benefit. In cases expected to require only a short duration of support for bridge to transplant, it may be appropriate not to correct moderate levels of aortic insufficiency.

This study has several limitations. First, the concomitant procedures are heterogeneous, ranging from closure of patent foramen ovale to valve replacement. Clearly, the additive risks for these items are probably also different. Grouping all concomitant procedures may therefore be suboptimal. Subgroup analysis helps to characterize outcome differences, but, with small numbers of patients, results in decreased statistical power.

Additionally, the long-term benefits of concurrent procedures on the native heart may vary substantially as LVAD designs change. For example, a patient with significant mitral insufficiency who is treated with a device that affords incomplete left ventricular unloading may experience clinical symptoms as the result of ongoing mitral insufficiency. On the other hand, if the LVAD achieves more complete left ventricular unloading either because of design or operational setting, the mitral insufficiency may not be clinically relevant. Therefore, the risks and benefits of concomitant procedures may vary from one device type to another and may also vary with the manner in which the devices are operated. This consideration limits the broader applicability of the results presented in this study.

Isolated HMII implants in the HMII BTT trial have a very low procedural mortality. Concurrent procedures such as closure of PFO and tricuspid procedures do not appear to add procedural risk, whereas implants with concurrent aortic procedures had a much higher mortality rates. Further investigation of LVAD implant procedures with concurrent cardiac procedures is warranted to better define the risk-benefit ratio.

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**Disclosures**

Drs John, Pagani, and Milano received research support from Thoratec Corporation. Dr Rogers received research support and serves as a clinical consultant for Thoratec Corporation. Dr Farrar is an employee of Thoratec Corporation.

**References**


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