Second INTERMACS annual report: More than 1,000 primary left ventricular assist device implants

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The Interagency Registry For Mechanical Circulatory Support (INTERMACS),1 a National Heart, Lung, and Blood Institute (NHLBI)-sponsored collaboration between the NHLBI, the United States (U.S.) Food and Drug Administration (FDA), the Center for Medicaid and Medicare Services (CMS), and the advanced heart failure/mechanical circulatory support professional community, began prospective patient enrollment and data collection on June 23, 2006. On March 27, 2009, CMS mandated that all U.S. hospitals approved for mechanical circulatory support as destination therapy (DT) enter mechanical circulatory support patient data into a national database, INTERMACS. The power of INTERMACS data stems from the mandatory data submission on all durable mechanical circulatory devices, a formal process for adverse event adjudication, dedicated innovative electronic data submission, data element design to create a template for comparison with medical therapy, rigorous data monitoring, hospital auditing through the United Network of Organ Sharing, and a formal process for data access and publications.

Since the inception of INTERMACS, an ongoing evolution of both strategies for device application and the types of available devices has continued to refine the landscape of mechanical circulatory support. Throughout this experience, the only device approved in the United States for permanent DT was the HeartMate XVE (Thoratec, Pleasanton, CA),2 a pulsatile ventricular assist device that is now known to frequently develop bearing wear and require device replacement within 2 years of implantation. Yet, in many countries outside the United States, newer axial flow and centrifugal flow rotary pumps provide long-term circulatory support. INTERMACS only collects data on devices that are FDA-approved for clinical use, and no adult rotary pump was approved in the United States for the first several years of the INTERMACS experience. The spectrum of devices entered into INTERMACS must also be viewed in the context of multiple concurrent U.S. clinical trials of continuous flow pumps implanted as bridge-to-transplant (BTT) therapy as well as permanent support. Thus, for the first 2 years, despite the rigorous requirements for data completeness and accuracy, INTERMACS was hampered by an inability to collect data on newer, more promising rotary pumps that were not yet FDA-approved.

The INTERMACS playing field changed dramatically in April 2008 when the HeartMate II axial flow pump (Thoratec) received FDA approval for clinical use as a result of the HeartMate II axial flow pump (Thoratec) receiving FDA approval for clinical use as a result of the...
BTT therapy in the United States. A portion of this report will examine the changing practice patterns in the application of device type (continuous flow vs pulsatile) and device strategies during the past 3 years. In fact, the genesis of INTERMACS, partly by chance and partly by design, uniquely positioned this database to observe, record, and analyze this historical transition—at least for the immediate future—from larger, powerful pulsatile pumps to the world of continuous flow technology, with the unproven promise of greater durability while retaining long-term patient functionality.

This report begins the process of long-term evaluation of continuous flow technology against the background of a large registry of detailed patient and device data based on pulsatile pump technology.

**Patient population**

Between June 23, 2006, and March 31, 2009, 88 institutions (Appendix 1) entered 1,420 patients into the INTERMACS database. Mean follow-up for survivors has been 6 months (range, 1 day to 2.9 months).

This report will focus on the 1,092 patients who received primary left ventricular assist device (LVAD) implants among the total of 1,420 patients who received primary and secondary devices (Table 1). The FDA-approved devices included in the INTERMACS registry are listed in Appendix 2. The general patient demographics were similar for all patients and the primary LVAD group (Table 2).

### Device type, severity of illness, and pre-implant strategy

The 1,092 primary LVAD implants were approximately 48% pulsatile and 52% continuous flow pumps (Table 3). At the time of implant, 85% of patients were in INTERMACS level 1 or 2 or 3, and less than 5% were higher than level 4 (Table 4). The spectrum of INTERMACS levels has changed during the course of the study; the proportion of level 1 has decreased from 38% during the first half of the study to 27% during the second half. This likely reflects a recognition of the higher early mortality associated with

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Prospective Patients (N = 1420) Who Received Primary and Secondary Devices (INTERMACS: June 2006–March 2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device side</td>
<td>Primary</td>
</tr>
<tr>
<td>LVAD</td>
<td>1092</td>
</tr>
<tr>
<td>RVAD</td>
<td>3</td>
</tr>
<tr>
<td>Bi-VAD</td>
<td>179</td>
</tr>
<tr>
<td>TAH</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>1324</td>
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</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Type of Primary Left Ventricular Assist Device (INTERMACS: June 2006–March 2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>N (N = 1092)</td>
</tr>
<tr>
<td>Pulsatile</td>
<td>528</td>
</tr>
<tr>
<td>Intracorporeal</td>
<td>460</td>
</tr>
<tr>
<td>Paracorporeal</td>
<td>68</td>
</tr>
<tr>
<td>Continuous flow</td>
<td>564</td>
</tr>
<tr>
<td>Total</td>
<td>1092</td>
</tr>
</tbody>
</table>

**INTERMACS, Interagency Registry For Mechanical Circulatory Support; LVAD, left ventricular assist device.**

<table>
<thead>
<tr>
<th>Table 4</th>
<th>INTERMACS Level at Implant for 1092 Primary LVAD (June 2006–March 2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERMACS level (pre-implant)</td>
<td>No.</td>
</tr>
<tr>
<td>1. Critical cardiogenic shock</td>
<td>328</td>
</tr>
<tr>
<td>2. Progressive decline</td>
<td>437</td>
</tr>
<tr>
<td>3. Stable but inotropic dependent</td>
<td>168</td>
</tr>
<tr>
<td>4. Recurrent advanced HF</td>
<td>106</td>
</tr>
<tr>
<td>5. Exertion intolerant</td>
<td>21</td>
</tr>
<tr>
<td>6. Exertion limited</td>
<td>12</td>
</tr>
<tr>
<td>7. Advanced NYHA III</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>1092</td>
</tr>
</tbody>
</table>

**HF, heart failure; INTERMACS, Interagency Registry For Mechanical Circulatory Support; LVAD, left ventricular assist device; NYHA, New York Heart Association.**

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*a* Of the 96 not primary implants, 40 (42%) have their primary implant entered into Interagency Registry For Mechanical Circulatory Support (INTERMACS).
implementation of mechanical circulatory support in the throes of cardiogenic shock\(^1\) (see Survival).

The distribution of pre-implant device strategies continues to focus on supporting patients to cardiac transplantation as bridge to candidacy (BTC) or BTT (Table 5). The initial strategy was permanent (DT) in nearly 10%. The distribution of INTERMACS levels among device strategies is summarized in Table 6.

### Survival

The superior survival of LVAD patients compared with survival with device types and combinations in this database is reflected in Figure 1. The focus of this report is the actuarial survival of the primary LVAD cohort, which was 83% at 6 months, 74% at 1 year, and 55% at 2 years (Figure 2).

The survival stratified by INTERMACS levels shows early increased death for patients in level 1 at the time of device implant (Figure 3). When stratified by device strategy, BTT patients had superior survival (Figure 4). In contrast with BTT and BTC cohorts, nearly all of the DT implants were pulsatile pumps, which does not reflect the more recent continuous flow technology (see later sections). Interpretation of these actuarial curves is further confounded by the censoring at transplantation, which is heavily weighted toward the BTT group. As shown in the competing outcomes analysis, 52% of BTT patients had undergone transplantation at 1 year (Figure 5) compared with 35% in the BTC group (Figure 6) and only 10% in DT patients (Figure 7).

### Causes of death

The primary causes of death for patients receiving primary LVAD implants are listed in Table 7. The major causes of death differed somewhat according to device strategy: central nervous system events accounted for nearly twice the proportion of deaths among DT patients as for BTT or BTC patients (Table 8). The reasons for this difference are not yet apparent.
Figure 2  Actuarial and parametric survival is shown for the 1,092 patients undergoing primary left ventricular assist device (LVAD) implant. Patients are censored at transplant or device explant for recovery. The dashed lines represent the 70% confidence limits. The hazard function (instantaneous risk of death) is depicted by the lower curve.

Figure 3  Actuarial survival is shown stratified by Interagency Registry For Mechanical Circulatory Support (INTERMACS) level at left ventricular assist device (LVAD) implant. The depiction is as in Figure 1.

Figure 4  Actuarial survival is shown stratified by device strategy at time of implant. The depiction is as in Figure 1. BTT, bridge to candidacy; BTC, bridge-to-candidacy; DT, destination therapy; LVAD, left ventricular assist device.

Figure 5  Competing outcomes are shown for primary left ventricular assist devices (LVAD) with bridge to transplant (BTT) as the strategy at the time of implant. At any time point in the follow-up, the sum of the percentages of all outcomes equals 100%.

Figure 6  Competing outcomes analyses are shown for primary left ventricular assist device (LVAD) patients with bridge to candidacy (BTC) as the initial strategy at the time of implant. The depiction is as in Figure 5.

Figure 7  Primary left ventricular assist device (LVAD) patients with destination therapy (DT) as the initial strategy at time of implant. The depiction is as in Figure 5.
Risk factors for death

By multivariable analysis, (see Appendix 3 for list of variables examined), risk factors reflecting older age, greater severity of right ventricular failure, and cardiogenic shock at implant predict a higher likelihood of early death among all LVAD patients (Table 9). It is of interest that the use of a pulsatile pump was a risk factor for death in the constant phase. Whether pump-related complications or malfunction account for this risk factor will require further analyses. Among the smaller group of DT patients (essentially all of whom received a pulsatile pump), older age was the only identifiable risk factor for death (Table 10).

Emergence of continuous flow technology

During the first 2 years of INTERMACS, few pulsatile pumps were entered into the registry. With the first FDA approval of a continuous flow pump for adults as BTT support in April 2008, these pumps became available for entry into INTERMACS. Patient accrual before and after approval of an adult continuous flow pump shows a dramatic change in favor of continuous flow devices (Figure 8). The preference for continuous flow technology as BTT therapy (currently no continuous flow pump is approved for DT) is reflected in the depiction indicating that more than 85% of primary LVADs implanted between July 2008 and
January 1, 2009, were continuous flow pumps. The survival advantage to date with continuous flow pumps (BTC or BTT) is apparent in Figure 9.

Adverse events

The profile of adverse events among primary LVAD patients is listed in Table 11. Because continuous flow pumps have only accrued a mean follow-up of 4.6 months, Table 12 compares adverse events among pulsatile vs continuous flow pumps during the first 6 months after implantation. Infection and bleeding remain the most common adverse events in the LVAD population in the first year after implant. In the BTT and BTC groups, the adverse events are different for the continuous vs pulsatile pumps. In general, the events per 100 patient-months are importantly reduced in patients with continuous flow devices for device malfunction, infection, hepatic dysfunction, and neurologic events.

Table 9 Risk Factors for Death after Implant in 1092 Primary LVADs (INTERMACS: June 2006–March 2009)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Early HR</th>
<th>Early p-value</th>
<th>Constant HR</th>
<th>Constant p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (older)</td>
<td>2.42a</td>
<td>&lt;0.0001</td>
<td>1.55a</td>
<td>0.0005</td>
</tr>
<tr>
<td>Bilirubin (higher)</td>
<td>1.41b</td>
<td>0.0002</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>RA pressure (higher)</td>
<td>2.08c</td>
<td>0.0009</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>1.97</td>
<td>0.02</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>BTC or DT</td>
<td>. . .</td>
<td>1.80</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Pulsatile pump</td>
<td>. . .</td>
<td>2.74</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

BTC, bridge to candidacy; BTT, bridge to transplant; DT, destination therapy; HR, hazard ratio; INTERMACS, Interagency Registry for Mechanical Circulatory Support; LVAD, left ventricular assist device; RA, right arterial.

*Hazard ratio denotes the increased risk from age 60 to 70 years.

Evolution of device strategy

The frequency with which patients are diverted from their original strategy was documented in the first annual INTERMACS report. Coincident with the availability of a continuous flow pump for BTT in adults in April 2008, a marked shift occurred away from a primary strategy of DT among patients entered into the registry (Table 13). The dramatic increase in the number of patients entered into the database with a primary strategy of BTT or BTC beginning in the second quarter of 2008 (Table 13) further underscores the seeming lack of clear distinction between primary device strategies. Close observation of these trends after FDA approval of a continuous flow device for DT will shed further insights into clinical practice.
Although INTERMACS requires strict adherence to data submission, identification of adverse events, and complete patient follow-up, the registry does not directly mandate specific clinical protocols for frequencies of routine patient visits, laboratory tests to be obtained, or functional outcomes and quality of life tests to be administered. However, INTERMACS does require that if any such tests are obtained, the results must be entered.

Areas of incomplete data submission

Although INTERMACS requires strict adherence to data submission, identification of adverse events, and complete patient follow-up, the registry does not directly mandate specific clinical protocols for frequencies of routine patient visits, laboratory tests to be obtained, or functional outcomes and quality of life tests to be administered. However, INTERMACS does require that if any such tests are obtained, the results must be entered.
The divergence in clinical practice for routine chemistries rather than periodic functional and quality of life testing is apparent in our follow-up data (Table 14). A review of routine blood chemistries collected at periodic intervals showed the rate of complete data submission was very high. In contrast, quality of life as measured by the EuroQol, cognitive function as measured by the Trailmaking Test, and functional outcome measured by the 6-minute walk test have been reported with a much lower frequency (Table 14).

Review of this issue at the recent annual INTERMACS meeting (March 27, 2009, Orlando, FL) revealed that these 3 simple tests—EuroQol, Trailmaking, and 6-minute walk—are not a routine part of the follow-up in many mechanical circulatory support centers. This deficiency has important implications as we attempt to collect data that will further define the benefits of this therapy compared with medical treatment or other strategies for patients with advanced New York Heart Association class III and IV heart failure. Future recommendations on the advisability of this expensive and invasive therapy will depend not only on survival advantage and freedom from adverse events but also, importantly, on the patient’s expected functionality, cognitive recovery, and quality of life with long-term mechanical circulatory support.

To address the problem of incomplete assessment of functional outcome and quality of life after device implant, a group of experts representing the International Society for Heart and Lung Transplantation, including experts from INTERMACS, has been convened to develop a consensus recommendation for the follow-up of mechanical circulatory support patients, focusing on functional evaluation, cognitive assessment, and quality of life measures.

### Summary

INTERMACS has analyzed the first 1000-plus patients with primary implantation of LVADs during a transitional period from pulsatile technology to continuous flow pumps. The shift toward implantation of axial flow technology since its approval by FDA is dramatic. This trend has been accompanied by continued fluctuation in the designation of primary device strategy as BTT, BTC, and DT. Inferences from this database regarding expected midterm survival with device therapy must be interpreted with this understanding. When continuous flow technology is routinely available for long-term DT, and as multiple continuous flow pumps are approved, INTERMACS offers a unique opportunity to compare and contrast these technologies in the setting of evolving indications, changing patient profiles, and refinement of device strategy in the developing landscape of mechanical circulatory support.

### Disclosure statement

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None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

### References

Appendix 1  Institutions That Have Contributed Data

Advocate Christ Medical Center
Allegheny General Hospital
Baptist Health Medical Center
Baptist Memorial Hospital—Memphis
Barnes-Jewish Hospital
Baylor University Medical Center
Brigham and Women's Hospital
Bryan LGH Medical Center
California Pacific Medical Center
Carolinas Medical Center
Cedars Sinai Medical Center
Children's Healthcare of Atlanta
Children's Medical Center
Cleveland Clinic
Columbia Presbyterian–Children's Hospital of New York
Columbia University Medical Center–New York Presbyterian
Duke University Medical Center
Emory University Hospital
Hahnemann University Hospital
Henry Ford Hospital
Hospital of the University of Pennsylvania
Inland Northwest Thoracic Organ Transplant Program, Sacred Heart Medical
Inova Fairfax Hospital
INTTEGRIS Baptist Medical Center
Intermountain Medical Center (formerly LDS Hospital)
Jackson Memorial Health System/University of Miami
Jewish Hospital
Lancaster General Hospital
Lankenau Hospital
Lutheran Hospital of Indiana
Maine Medical Center
Massachusetts General Hospital
Mayo Clinic Hospital
Mayo Clinic Jacksonville
Medical City Dallas Hospital
Methodist Hospital
Methodist Specialty and Transplant Hospital
Mid America Heart Institute of Saint Luke's Hospital
Montefiore Medical Center
Morristown Memorial Hospital–Atlantic Health
Mount Sinai Medical
Newark Beth Israel Medical Center
Northwestern Memorial Hospital
Ochsner Medical Center
Oregon Health & Science University
OSF St Francis Medical Center
Penn State Milton S. Hershey Medical Center
Robert Wood Johnson University Hospital
Rush University Medical Center
Saint Marys/Mayo Clinic
Sentara Norfolk General Hospital
Seton Medical Center
Shands at the University of Florida
Sharp Memorial Hospital
St. Louis Children's Hospital
St. Luke’s Episcopal Hospital/Texas Heart Institute
St. Luke’s Medical Center
St. Vincent Hospital and Health Care Center
Sutter Memorial Hospital

Appendix 1  Continued

Tampa General Hospital
Temple University Hospital
Texas Children's Hospital
The Johns Hopkins Hospital
The Methodist Hospital
The Ohio State University Medical Center
Thomas Jefferson University
Tufts Medical Center
University Health Care
University Hospitals Case Medical Center
University of Alabama at Birmingham Hospital
University of Arizona Medical Center
University of California–Los Angeles Medical Center
University of Chicago Hospitals
University of Colorado Hospital
University of Iowa Hospitals and Clinics
University of Maryland Medical Center
University of Michigan Health Systems
University of Minnesota Medical Center–Fairview
University of North Carolina Hospitals
University of Pittsburgh Medical Center
University of Rochester Medical Center (Strong Memorial Hospital)
University of Texas Southwestern Medical Center
University of Virginia Health System
University of Wisconsin Hospital and Clinics
Virginia Commonwealth University Health System
Washington Hospital Center
Weill Cornell Medical Center/New York Presbyterian Medical Center
Westchester Medical Center
Appendix 3  Variables Examined in Risk Factor Analysis

Demographics
- Age
- Male
- White
- Black
- Height, cm
- Weight, kg
- Body surface area (BSA)

Laboratory values
- Sodium
- Albumin
- Bilirubin
- Blood urea nitrogen (BUN)
- Creatinine
- Cholesterol
- International normalized ratio (INR)

Clinical
- Protein C
- C-reactive protein (CRP)
- Blood type
- Diagnosis—congenital
- Diagnosis—coronary artery disease
- History of coronary artery bypass grafting (CABG)
- History of valve
- History of mechanical circulatory support devices (MCSD)
- Implantable cardiac defibrillator (ICD)
- Inotropes
- Diabetes
- Chronic obstructive pulmonary disease (COPD)
- Ascites
- Cardiovascular accident
- Cancer
- Current smoker
- Alcohol abuse
- New York Heart Association (NYHA)

Device strategy
- Bridge to recovery
- Bridge to transplant listed
- Bridge to transplant likely listed
- Bridge to transplant moderately likely
- Bridge to transplant unlikely
- Destination therapy

Appendix 3 Continued

Hemodynamics
- Cardiac output
- Left ventricular end-diastolic diameter (LVEDD)
- Pulmonary diastolic pressure
- Pulmonary systolic pressure
- Pulmonary wedge pressure
- Right ventricular ejection fraction (RVEF)
- Right atrial pressure (RAP)
- Systolic blood pressure
- Left ventricular ejection fraction <20

Patient profile levels
- Level 1
- Level 2
- Level 3
- Level 4
- Level 5
- Level 6
- Level 7

Ventricular tachycardia/ventricular fibrillation

Implant information
- Left ventricular assist device (LVAD)
- Right ventricular assist device (RVAD)
- Biventricular assist device (Bi-VAD)
- Total artificial heart (TAH)
- Concomitant surgery
- Left ventricular assist device continuous flow