Advances in Mechanical Circulatory Support

Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)
What Have We Learned and What Will We Learn?

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The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is a North American national registry for mechanical circulatory support devices (MCSDs) that are used to treat advanced heart failure. Durable MCSDs that have been approved by the US Food and Drug Administration (FDA) are included in this registry; however, MCSDs that remain in FDA trials pending initial approval (ie, investigational device exemption [IDE] trials) and devices intended for short-term use (eg, Abiomed BVS 5000 ventricular assist device [Abiomed, Danvers, MA]) are not included. The purposes of this article are to present a developmental history of INTERMACS, to outline the collaboration of INTERMACS with various constituencies (eg, FDA, National Institutes of Health, Center for Medicare & Medicaid Services, industry, and physicians), to present a summary of information generated to date by INTERMACS, and to describe the future directions of INTERMACS.

Developmental History of MCSDs and INTERMACS

The concept of using mechanical circulatory assistance for more than a brief time after a cardiac operation dates to the early 1960s with the development of MCSDs that fit the definitions of counterpulsation devices (eg, the intra-aortic balloon pump), ventricular assist devices (VADs), and total artificial hearts. The development and initial clinical evaluation of these devices were regulated by individual academic medical center review groups that evolved into institutional review boards. The FDA entered this arena in 1976 with the advent of the FDA section for device regulation based on passage of the 1976 Medical Device Amendments. By 1991, groups including the Institute of Medicine foresaw the need for a detailed longitudinal database for patients receiving MCSDs, stating in an Institute of Medicine report that "patients should be followed through a registry for the remainder of their lives...." The committee further recommended that the National Heart, Lung, and Blood Institute support long-term follow-up studies.

Eventually, a competitive contract was issued by the National Institutes of Health in collaboration with the FDA to record and analyze patient outcomes with durable MCSDs. The group chosen to fill the contract included 3 coprincipal investigators—James K. Kirklin, MD, James B. Young, MD, and Robert L. Kormos, MD—working in collaboration with the United Network for Organ Sharing and others. Advice on constructing such a registry was requested from experts in the field of mechanical circulatory support, many of whom had previously worked on similar projects under the auspices of the International Society for Heart and Lung Transplantation (ISHLT). During the initial meetings of these MCSD experts, the name INTERMACS was chosen. These initial meetings also outlined the organization of the group and established the goals of INTERMACS.

For the first time, there was a concerted effort by physicians and industry partners to define adverse events so that the outcomes for patients with any durable MCSD would be gathered and adjudicated in uniform fashion. The goal was to provide information that allows optimal MCSD-patient matching and objective quantitative evaluations of blood pumps as they move from IDE trials into postmarket approval surveillance of clinical use. In similar fashion, a classification system was created to describe the preoperative condition of the patient that was relevant to selection for MCSD therapy. The classification system provides meaningful operational definitions that are essentially subclassifications of New York Heart Association class III and IV functional status. These profiles of patient disease severity at implantation are designated INTERMACS levels 1 (critical cardiogenic shock) through 7 (advanced New York Heart Association class III symptoms). Other patient descriptors include a group of demographic variables and the intended device strategy at implantation. It is important to note that participation in a recognized multi-institutional registry such as INTERMACS is mandatory for Center for Medicare & Medicaid Services funding of MCSD implants as destination therapy. Moreover, failure of an individual site to adhere to requirements for participation in INTERMACS (eg, timely and accurate data entry, prompt query response) can lead to exclusion of a participating site until the deficiencies are rectified.
INTERMACS: Accomplishments to Date

Since its inception, INTERMACS has generated information that is useful to its community of collaborators (eg, outcomes data for quality improvement at individual programs) and provides perspective for other publications in the field of mechanical circulatory support (eg, publications that describe the results of multicenter IDE trials for VADs). INTERMACS has published a series of annual reports; the first annual report was published in 2008 with reports every year thereafter through 2012.

During the first year of INTERMACS, enrollment actuallyspanned June 23, 2006, to December 31, 2007, and the statistical methods developed for the initial report became the template for subsequent INTERMACS reports. One such method is multivariate analysis, which was used to define risk factors for death in patients with MCSDs. In the first annual report, older age, the presence of ascites at the time of implantation, and increased serum bilirubin were associated with death after MCSD placement. The adverse effects of cardiogenic shock and hemodynamic instability were established early in the history of INTERMACS by showing substantially diminished survival of patients in INTERMACS level 1 (ie, cardiogenic shock) compared with other patient classifications. Another method, competing outcomes analysis, was used to depict the proportions of patients experiencing the following outcomes after MCSD implantation: alive and on MCSD support, dead, device explanted because of recovery of the native heart, or status post–cardiac transplantation (Figure 1). Publication of this information in quarterly reports reinforces the message of INTERMACS and gives timely updates to participants.

The second year of INTERMACS was contemporaneous with FDA approval of a continuous-flow pump as a bridge to transplantation (HeartMate II left VAD; Thoratec Corp, Pleasanton, CA; April 2008). Subsequent INTERMACS annual reports documented the rapid adoption of continuous-flow technology and the concomitant marked decrease in the use of pulsatile pump designs. By the time of the third INTERMACS annual report, the rate of device implantation in the United States was accelerating, and the majority of these implants were continuous-flow left VADs. Importantly, the profile of patients undergoing VAD implantation shifted from critical cardiogenic shock (ie, INTERMACS level 1) to progressively declining heart failure despite medical therapy (ie, INTERMACS levels 2 and 3). For example, in the period from June 2006 to December 2008, 34.7% of implants were for INTERMACS level 1 (patients in shock) with 40% of patients categorized as INTERMACS level 2 (progressively declining heart failure). In the subsequent period of January 2009 to June 2010, only 17.3% of patients were INTERMACS level 1 at the time of initial implantation, whereas 45.2% were INTERMACS level 2. With a larger number of patients and longer follow-up, refinement of risk modeling became possible. For example, the risk factors for death were divided into early hazard and constant hazard phases in the third INTERMACS annual report. Early-phase risk factors included critical cardiogenic shock, higher blood urea nitrogen level, concomitant surgery at the time of MCSD implantation, and requirement for biventricular assistance. Constant (late)-phase risks for death in this report included older age, diabetes mellitus, pulmonary hypertension, lower serum sodium at the time of implantation, and use of a pulsatile-flow left VAD.

The fourth INTERMACS annual report passed the milestone of enrolling >4000 patients in the database. During the era of the fourth report ending June 30, 2011, there was persistent migration away from the use of pulsatile VAD technology and a decrease in the use of durable VADs for patients classified as INTERMACS level 1. Unfortunately, data are not collected by INTERMACS for patients who undergo evaluation for mechanical circulatory support but do not receive a durable MCSD. The types of devices or management strategies used in these INTERMACS level 1 patients and their outcomes are unknown beyond single-institution reports or multicenter studies supported by industry for an individual MCSD. Furthermore, the hypothesis that patient survival can be improved by converting a patient from INTERMACS level 1 to 2 with the use of temporary mechanical circulatory support (eg, Impella 5.0 left VAD [Abiomed] or extracorporeal membrane oxygenation) remains untested. It is interesting to note that as the prevalence of patients classified as INTERMACS level 1 at the time of implant decreased, other factors associated with increased patient risk for death became more common (eg, older age at the time of implantation and the presence of prior cardiac surgery). Thus, it appears that high-risk patients are not avoided. Rather, physicians are accepting patients for mechanical circulatory support with risks other than hemodynamic instability and cardiogenic shock.

The INTERMACS database has been used to address several important questions in the field of mechanical circulatory support. One such article is an assessment of infection in MCSD patients. A 2010 report by Holman et al...
documented the continued presence of infection as a relatively frequent adverse event for MCSD patients despite attempts to prevent it. Moreover, the adverse influence of infection on survival was demonstrated in the absence of full-blown sepsis or sepsis syndrome, which had previously been shown in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Trial.22 The time until the first infection adverse event was examined, and infection was shown to be more common in the initial 3 months after MCSD implantation than in the subsequent time period (Figure 2). Patients who suffered their first infection adverse event before 1 month after implantation had significantly worse survival compared with patients who had their first infection adverse event later. Other risk factors for infection adverse events included older age (dichotomized at 60 years of age; Figure 2), INTERMACS level 1 status before surgery (Figure 3), the requirement for biventricular mechanical circulatory support, and higher blood urea nitrogen levels.21

Another important question is the influence of sex on outcome after placement of durable left VADs. In an analysis published in 2012, Hsich and coauthors23 examined the influence of sex on survival and adverse events after left VAD implantation. This group found that at a mean follow-up time of 7 months, there were no statistically significant differences in survival for men and women in either nonadjusted or risk-adjusted analyses. When one sums the patients alive on mechanical support, transplanted, and recovered with pump removal, it becomes apparent that the majority of patients are alive at 6 months after VAD placement in the current era, regardless of sex (77% for women and 83% for men; Figure 4A and B). With regard to adverse events, there were no statistically significant sex-based differences in the time to first infection, bleeding adverse events, or device malfunction. However, female patients were at increased risk for neurological adverse events.

Several abstracts have been presented at national and international meetings that are based on analyses of INTERMACS data. These studies addressed questions important to the community of physicians who use left VADs and engineers who design them. Examples include determining whether the incidence of early neurological adverse events has changed since the introduction of continuous-flow technology and quantifying the effects of preimplantation nutritional state and hepatic function on postimplantation patient outcome. Another presentation determined whether the lower survival rate in patients requiring biventricular VAD support is related to MCSDs or patient risk factors.24

The number of children supported with durable VADs remains low relative to adults. However, there are now a sufficient number of pediatric patients to initiate INTERMACS-based analyses of outcomes in pediatric patients supported with pediatric-specific MCSDs. The presence of robust outcome data is essential for measuring patient outcomes, reviewing the emerging field of pediatric mechanical circulatory support, and evaluating novel pediatric-specific devices.25 INTERMACS analyses are evaluated in light of single-institution studies and published results of FDA IDE trials, both of which appear before publications from INTERMACS because INTERMACS is limited to data from FDA-approved MCSDs.

INTERMACS is now in its second contractual period with the National Institutes of Health, and the funding sources for this work are evolving away from governmental agencies. Specifically, fees are now paid by implanting sites and industrial partners to participate in INTERMACS. Payment of fees entitles each group to receive site-specific or device-specific INTERMACS information that is crucial to quality assessment and quality improvement efforts at implanting sites and is similarly important to the evaluation and further development of MCSDs by industry. Ultimately, it is expected that this information will lead to increased MCSD effectiveness and safety.
INTERMACS: What Will the Future Hold?

INTERMACS is important to the postmarketing surveillance of MCSDs and provides a paradigm for postmarket approval surveillance of other medical devices such as internal cardioverter-defibrillators. As the field of MCSD moves forward, INTERMACS data will continue to identify risk factors for patient mortality and morbidity during circulatory support. This information will help to formulate novel methods that nullify these risks. Possible approaches include changes in surgical and medical management techniques, changes in the engineering of existing MCSDs, and the development of completely novel MCSDs.

One goal of INTERMACS at its inception was to provide timely information on patient outcomes for use in evaluating new MCSDs. Some groups now use INTERMACS data as the comparison arm in clinical trials, although the use of registry data for this purpose has limitations compared with clinical trials for MCSDs that are prospectively randomized to medical therapy or to an approved MCSD. Aspects of INTERMACS that distinguish it from a typical registry include the following items. There are criteria for inclusion in INTERMACS (eg, each site must be approved by INTERMACS, and only MCSDs that are durable and approved by the FDA are included). The definitions for adverse events were developed through the collaboration of physicians, industry, and the regulatory community. Importantly, the adverse event definitions for INTERMACS are used uniformly for all MCSDs so that patient outcomes can be compared between MCSDs. Entries for MCSD implants are compared with records from manufacturers to ensure complete reporting of all cases. The reports from manufacturers are received by INTERMACS on a quarterly basis. INTERMACS does not accept incomplete case report forms, thereby ensuring complete data entry. Completeness of follow-up of patients is monitored by the Data Coordinating Center for INTERMACS. Form completion rates of $<90\%$ trigger a phone call to the local site investigators to improve follow-up. Lack of remediation can lead to expulsion of the site from INTERMACS. Data are screened at the time of entry to detect outliers that may represent mistakes (eg, serum creatinine of 17 instead of 1.7 mg%), and there is an annual telephone audit for each site. INTERMACS data are frozen (ie, no modification of entered data) every 6 months with a 1-month grace period for data completion before freezing. Regulatory requirements for INTERMACS are as follows: compliance with HIPPA regulations, human subjects training for site investigators, and local institutional review board approval for participation of individual sites, including informed consent from the patient. Outcomes, including adverse events, are adjudicated by experts in the field of advanced heart failure and mechanical circulatory support. Two experts provide initial adjudication. If there is disagreement at the initial review, it is resolved by a member of the INTERMACS Adverse Event Committee acting as a third reviewer. An Observational Study Monitoring Board provides oversight for INTERMACS. The Data Access, Analysis, and Publication Committee reviews requests for research projects based on the INTERMACS data. That committee then partners with study investigators and the Data Coordinating Center to perform thoughtfully planned analyses.

The first use of INTERMACS data as the comparison arm for an IDE trial was presented to an FDA Circulatory System Devices Advisory Panel by HeartWare, Inc on April 25, 2012. The FDA Executive Summary and Questions for the Circulatory System Devices Advisory Board Panel are interesting because they outline the development of a new paradigm for the evaluation of medical devices using registry (ie, INTERMACS) data to define clinical expectations for a noninferiority trial.

The Executive Summary set the agenda for this new approach with the statement:

This is the first left ventricular assist device (LVAD) trial for which data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is being used as a contemporaneous control. This memorandum summarizes FDA’s review of the postmarket approval and highlights the particular areas for which we are seeking your input. These topics include the safety and effectiveness profile of the device as demonstrated by the results of the clinical study conducted by the Sponsor, includ-
ing a comparison of its benefit to risk profile to data in a registry of currently marketed devices for the same indication.29

Moreover, the Executive Summary described a conservative approach to this initial venture with INTERMACS data by stating its limitations:

The IDE study was designed to evaluate noninferiority of the proportion of study patients alive, transplanted, or explanted for recovery at 180 days to the same proportion obtained from the INTERMACS cohort. The study’s statistical plan allowed for a traditional, PG (performance goal)-based primary end point analysis if it was determined that the patients in the two study arms were not similar enough in baseline characteristics to justify a treatment-control comparison.29

The Executive Summary further recognized potential pitfalls of comparisons to the INTERMACS population:

FDA accepted that the trial design incorporated differing degrees of specificity with regard to the characterization of the two arms’ inclusion and exclusion criteria. FDA believes that the HeartWare VAS (Ventricular Assist System) treatment arm of the trial was comprised of a more narrowly defined patient population than was in the INTERMACS control arm (eg, lack of recent cardiac events, designation of pulmonary hypertension). Furthermore, some of the analogous criteria could conceivably have allowed for enrollment of patients into the control arm with relatively worse clinical presentation than in the HeartWare VAS arm (eg, degree of renal impairment, degree of pulmonary impairment). Accordingly, FDA believes that appropriate clinical balance between groups for the eight prespecified propensity score covariates…may be quite important when considering the overall comparability of the HeartWare VAS and INTERMACS patients at baseline.

As mentioned previously, although identically defined INTERMACS events data were collected for both the treatment and control arm patients, the protocol did not prespecify any consideration of the adverse events rates of the control arm or consequently any direct comparison of event rates between the HeartWare VAS treatment and INTERMACS control arms. Justification at the time of the protocol design included differing methods of handling events (monitoring and adjudication for the treatment arm versus auditing and adjudication of events in the registry control arm).29

The advantages and disadvantages of INTERMACS for premarket approval and postmarket surveillance have yet to be fully defined. At this time, the perceived disadvantages include the dominance of INTERMACS by 1 pump design (HeartMate II left VAD; Thoratec) and the less rigorous monitoring of case report forms and source documents by INTERMACS compared with monitoring of data for a prospective randomized clinical trial. Moreover, the putative advantage of INTERMACS in expediting the premarket approval process (ie, serving as the comparison group for FDA IDE trials) has not been proven, although there is the potential to benefit the development cycle time for MCSDs.

The final frontier for MCSD registries is to cross geographic borders. Databases outside of North America for MCSDs include the European registry (EuroMACS), the Japanese mechanical circulatory support database (J-MACS), the French mechanical circulatory support database, the British mechanical circulatory support database, the Belgian mechanical circulatory support database, and others. In 2011, the ISHLT under the leadership of James Kirklin and David Naftel began talks with these groups to consolidate these registries into a single global effort called the ISHLT Mechanical Assisted Circulatory Support Registry (IMACS). Talks to establish IMACS continued at the ISHLT meeting in Prague in April 2012 to expand the reach of participating physicians, engineers, and members of the business and regulatory communities to a global level.32

Disclosures
Dr Holman has served on Data Safety and Monitoring boards for Levitronix (Waltham, MA), HeartWare, Inc (Framingham, MA), and Medtronic (Minneapolis, MN). He was a consultant for Abiomed (Danvers, MA).

References


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