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INTERMACS and MedaMACS: How Will They Guide Future Therapy?

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Abstract The INTERMACS registry has played a central role in the evolving field of device therapy for advanced heart failure (HF). This nationwide, prospective registry of approved assist devices has defined the boundaries of mechanical support, tracked the evolution from pulsatile to continuous flow, developed new profiles for advanced HF, and standardized adverse event definitions. INTERMACS has guided current therapy and in the future will do so aided by new insights from MedaMACS, a parallel registry of medically-managed ambulatory patients with advanced HF. Together INTERMACS and MedaMACS will leverage the power of observation research to guide patient-centered decisions about mechanical circulatory support.

Keywords Heart failure · Heart assist devices · Cardiomyopathy · Registries · INTERMACS · MedaMACS · Therapy

Introduction

Mechanical circulatory support (MCS) devices are now in widespread use for the treatment of advanced heart failure (HF) [1, 2]. After nearly half a century of clinical development, the pace of progress has accelerated dramatically in recent years, creating new challenges in candidate selection and clinical management amidst ongoing debate about the cost-effective use of health care resources. Although traditional randomized trials have played a pivotal role in the clinical development of contemporary MCS devices, post-marketing registries have become integral to this rapidly evolving field.

The Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) has leveraged the power of observational research to become a model for device registries across the world [3]. The knowledge gleaned from the INTERMACS experience has informed every phase of clinical MCS care, from candidate selection to perioperative and longitudinal clinical management [4]. INTERMACS has also served as a registry-based control arm for a pre-marketing study that resulted in Food and Drug Administration (FDA) approval of a novel ventricular assist device (VAD) [5•]. With the completion of the first five-year phase of INTERMACS, the boundaries of device therapy have been defined and extended, with improving long-term outcomes allowing interest to shift toward placement of MCS into "less sick" advanced HF patients [6–8, 9••]. While INTERMACS has already guided current therapy, in the future it will do so aided by new insights from a parallel registry of ambulatory patients with advanced HF receiving medical management. In 2013 the Medical Arm of Mechanically Assisted Circulatory Support, or MedaMACS, will begin studying the characteristics, preferences and outcomes of ambulatory patients with advanced HF who have not yet received MCS. The MedaMACS registry has already completed a successful screening pilot, laying the foundation for the larger nationwide registry [10–12]. Together MedaMACS and INTERMACS will survey the landscape of advanced HF and MCS therapy.

Registering a Revolution

In 1991 the Institute of Medicine recommended that the National Heart Lung and Blood Institute (NHLBI) maintain a registry of mechanical support devices as a routine aspect

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of care given the unique dependency of patients on device therapy. By the mid 1990s, pulsatile VADs had improved outcomes such that permanent device therapy was contemplated for advanced HF patients. The landmark REMATCH trial demonstrated significantly improved outcomes at 1- and 2-years with the HeartMate XVE compared to medical therapy in patients ineligible for transplant [13]. With the subsequent Centers for Medicare and Medicaid Services (CMS) coverage decision for destination therapy (DT) LVAD in 2003, the immediate need for a nationwide registry became apparent. As a condition for DT coverage, CMS required all patients to be entered in a nationally audited registry as part of Joint Commission certification so that long-term outcomes could be recorded and quality reports produced for hospitals [14]. In 2005 INTERMACS came to be thanks to collaboration between NHLBI, the Food and Drug Administration (FDA), CMS, industry, and academia.

Based at the University of Alabama at Birmingham, INTERMACS is now the national registry for FDA-approved circulatory support devices and has been prospectively registering this technology since June 2006. The specific goals of INTERMACS were to collect and disseminate quality data on MCS devices to improve patient selection and management, advance the development and regulation of next generation devices, and enable research into heart failure and recovery [15•]. Rolling publication of enrollment information and outcomes in quarterly reports provides timely updates for participating hospitals, industry, and the FDA. To date INTERMACS has enrolled more than 8500 subjects from over 140 participating sites and has resulted in multiple high-impact publications and presentations involving over 100 co-authors [16]. INTERMACS has been a model for a new registry of device therapy in children (PEDIMACS). In addition, databases for MCS have been developed in Japan, Britain, Belgium, France and other countries, following the INTERMACS example. A unified repository called the ISHLT Mechanical Assisted Circulatory Support Registry (IMACS) was established in 2011 to harvest data from the global MCS experience, offering a unique collaboration across national boundaries in an effort to advance the field [17].

Complementary Roles for Registries and Clinical Trials

Registries and clinical trials have overlapping goals, yet their unique features make each critical to the progress of MCS. In the pre-marketing phases (phase II and III) of clinical development, clinical trials are paramount. Clinical trials tend to be expensive, shorter in duration, and designed to explore a set number of pre-defined hypotheses about one or two devices, often from the same industry sponsor. Device implants in trials typically occur at select, high-volume clinical centers involving small cadre of investigators. The strict inclusion and exclusion criteria of clinical trials ensure internal validity, but may impair the ability to generalize results about both efficacy and safety outside the carefully controlled trial environment. A distinct strength of clinical trials comes in carefully defined endpoints and adverse events, which are strictly and independently adjudicated, with frequent auditing and oversight of data collection.

In contrast, registries like INTERMACS are designed to span a longer follow-up period and to explore a wide range of hypotheses, including ones that were pre-defined and others generated based on dynamic tracking of device applications [18]. Registries have broad entry criteria meant to offer a nationwide, real-world perspective of device therapy. INTERMACS has already played a role in both pre-marketing and post-marketing (phase IV) clinical investigations. INTERMACS targets all FDA-approved MCS devices in the United States and, based on screening logs and industry reconciliation, enrolls over 86 % of eligible patients [18]. The high enrollment rate is a function of deliverables the registry can provide to industry, regulatory (FDA), DT payers (CMS), clinicians and hospitals.

Like a trial, INTERMACS has an informed consent process and strict data security and confidentiality measures in place, along with oversight by an observational study monitoring board. Endpoints and adverse events are strictly defined in INTERMACS, but major events are subject only to medical review, rather than independent chart adjudication, and auditing is less frequent given the national scope of a registry involving over one hundred implanting centers. Randomized control trial data is frozen at enrollment, while INTERMACS evolves with the field, providing timely updates on the successes and complications of approved devices. While INTERMACS strives for data quality that approaches that of a rigorous clinical trial, it surpasses any clinical trial in national coverage, extended follow-up, and the ability to compare different pump platforms across multiple indications and timeframes, mapping the entire landscape of the MCS experience [18].

Impact of INTERMACS on Clinical Care

The INTERMACS registry has thus far been responsible for a number of signature achievements that have altered clinical practice. From new HF patient profiles to novel insight into device infection and strategies of deployment, INTERMACS has helped to define the standards of care of MCS (Table 1).

Patient Profiles

The INTERMACS profiles for MCS were developed because the broad NYHA class IV designation failed to provide an adequate description of clinical disease to allow optimal selection for current advanced therapies. While some New

Table 1 INTERMACS contributions

• Establishment of INTERMACS profiles to classify advanced heart failure
• Reveal practice patterns shifting away from implantation in the sickest profile 1 patients
• Map the transition from pulsatile to continuous flow devices and the rise of destination therapy
• Identify that strategic designations for implant are often fluid for a given patient
• Standardize adverse event definitions for device therapy
• Show the adverse impact of driveline infection in the absence of full-blown sepsis
• Sex-differences in mortality after LVAD have been attenuated by continuous flow pumps
• Develop recommendations for assessing function and quality of life with mechanical support
• INTERMACS used as a contemporary registry control group for an FDA IDE (investigational device exemption) clinical trial

York Heart Association (NYHA) class IV patients may be in critical cardiogenic shock with limited prognosis, death may not be imminent in others with resting symptoms. The labile NYHA classes only represent a snapshot of disease burden. By contrast, the INTERMACS profiles are a convenient short-hand integrating severity of illness and tempo of development by adding a modifier for arrhythmia burden and recurrent HF hospitalization [19]. The INTERMACS profiles are assigned by experienced clinicians over time to patients failing medical therapy and range from profile 1 (cardiogenic shock) to profile 7 (advanced NYHA class III). Currently, nearly 80 % of MCS devices are implanted in patients who are inotrope dependent or have worsening end-organ function (profiles 1–3) [9••].

INTERMACS patient profiles have been integrated into clinical practice to allow communication with colleagues, to adjust for perioperative risk, and to define target populations for future device studies. Sicker INTERMACS patient profiles have been consistently associated with higher perioperative morbidity and mortality [20, 21•]. By contrast, less acutely ill patients limited by advanced HF have better short- and long-term survival and shorter lengths of stay compared to patients in INTERMACS profile 1. For the last 3 years, the field has moved away from implanting durable LVADs in patients with profile 1 because of poor reported outcomes due to futility in most cases. The proportion of the sickest LVAD recipients (profile 1) has declined from 46 % to just 14 %, a trend paralleled by better renal function and nutritional status in LVAD recipients in recent years [9••, 22]. The increased clarity in clinical profiling has also prompted many centers to favor temporary circulatory support strategies to stabilize the multi-organ system disarray associated with cardiogenic shock prior to definitive MCS surgery. From the broad NYHA class IV designation, INTERMACS profiles have sorted patients into smaller specific groups with distinct outcomes.

Control Arm for Pre-Marketing Studies

Approval of MCS devices for the bridge-to-transplant indication has never been supported by a randomized trial. Of the three devices approved for the bridging indication, two offered no control population and another used a small historical control from the same institution [23, 24]. The ADVANCE trial of the HeartWare HVAD raised the standard for bridging approval by prospectively comparing outcomes with the new device compared to contemporary registry controls with other devices currently available for left ventricular support [5•]. The criteria for entry into the investigational device trial were the same for selection of the control patients from the INTERMACS registry. However, adverse event reporting was not specifically aligned between the trial and registry, and could not be specified by brand of device used according to prior agreement.

The challenge of using registry controls was evident in the ADVANCE study after the level of illness at implant was scrutinized. Profile 2 patients ("sliding on inotropes") accounted for 52 % of the control arm but only 24 % of the investigational arm, with a conversely higher proportion of the more stable profile 3 patients in the investigational arm (52 %) compared to controls (21 %), creating an unintended bias to less severe illness in the trial arm. Nevertheless, post hoc comparison indicated equivalent outcomes for each separate profile in the two arms of the study. The data from ADVANCE showed convincing non-inferiority of the HVAD compared to contemporary LVAD therapy. Indeed, by incorporating INTERMACS as a control group, the trial established a potential benchmark for bridging approval of a 90 % survival on device or transplantation by one year [25]. INTERMACS will allow ongoing contemporary surveillance of outcomes to determine when the bar should be raised for bridging approval.

Adverse Event Definitions

Throughout the evolution of mechanical support, improvements in survival have been offset by concerns about adverse events. Common safety concerns with MCS include neurologic dysfunction from strokes due to synthetic materials in the systemic circulation, bleeding from anticoagulant therapy or acquired coagulopathy, device malfunction, and infection

[9••]. Major clinical trials have used variable adverse event definitions, largely due to differing manufacturers, indications, and target populations. Prior to INTERMACS, it was a challenge to make meaningful comparisons between devices, centers, and patients. INTERMACS standardized adverse event definitions in collaboration with FDA and industry so that the most important complications in approved devices can be tracked in real time. These adverse event definitions have also allowed the development performance measures for accreditation of device programs across the United States.

Assist Device Infection

Device-related infection has been described as the Achilles heel of MCS [26]. Most infections involve the percutaneous driveline, pump pocket or both. Such infections are seldom curable and only treatable with chronic antibiotic suppression or pump explant with or without transplantation, making device infection a particular concern for the growing number of DT VAD recipients. Early data from INTERMACS spanning the pulsatile and non-pulsatile pump eras demonstrated the adverse influence of infection on outcome even in the absence of frank sepsis. Patients with their first infection less than one month after implantation had significantly worse survival than those with later infection [27]. Specific risk factors for device infection included INTERMACS Profile 1, renal failure, and the need for biventricular support.

More recent data from smaller continuous flow LVADs tracked in INTERMACS revealed a 19 % risk of percutaneous site infection by one year after implant [28]. Driveline infection was the third most common type of infection after sepsis and localized non-device infection. The peak incidence of percutaneous infection occurred 6 months after implant. Young age was the only adjusted risk factor, suggesting that mobility and independence in the outpatient setting may contribute to percutaneous infection risk [28]. Absence of percutaneous site infection was again linked with improved survival. There was no information on specific organism, treatments, or rates recurrent infection, highlighting the limits of registry-based data. Nevertheless, the story of device infection shows how the nationwide scope and mandatory reporting in INTERMACS make it a useful repository for tracking major adverse events and targeting remediation efforts.

Gender and LVAD Support

Early MCS studies of pulsatile devices suggested an increased mortality in women after LVAD and higher bleeding risk, though few studies enrolled significant numbers of female recipients [29, 30]. Even with expanded use in female patients thanks to the development of smaller, next-generation continuous flow pumps, sex-specific outcomes were difficult to analyze since the pumps were approved on the basis of two pivotal trials in which <20 % of participants were women. INTERMACS provides the ideal setting to evaluate the impact of recipient sex on LVAD outcomes. Using data from INTERMACS that included 401 female LVAD recipients (81 % continuous flow), Hsich and colleagues evaluated the link between pre-implantation characteristics and subsequent outcomes after a mean follow-up of 7 months [31]. There were no significant sex differences in mortality, infection risk, or bleeding after VAD. Women appeared have a modestly higher risk of first neurological event HR 1.44 (95%CI 1.05-1.96). The disparity of LVAD outcomes between the sexes has diminished dramatically with non-pulsatile devices. These data allayed concerns about implanting women with advanced HF, particularly those requiring urgent or emergent mechanical support. The study also illustrates how INTERMACS can be used as a platform for answering important unresolved questions about patient selection for device therapy using granular, statistically powerful, patient-level data.

Destination Therapy and the Future of MCS

The use of LVADs as permanent replacement therapy has increased over ten-fold since the approval of a continuous-flow device in early 2010 for DT, a trend documented by INTERMACS [32]. For the first time, a meaningful population of patients is receiving lifetime mechanical support, representing 34 % of all device implants in the most recent time interval [9••]. Given ongoing donor organ scarcity and improving LVAD outcomes, recipients of LVAD therapy who are not transplant candidates at implant are often being prepared for lifetime mechanical support. There remains ongoing debate about whether the MCS field should move beyond the artificial pre-implant strategic distinctions that have constrained trial design and defined reimbursement, toward an MCS indication of therapy for HF encompassing both bridge to decision and lifetime therapy [33, 34•].

Mechanical support may be on track to compete with transplantation for survival and quality of life for intermediate-term support. Data from the INTERMACS registry suggest that patients receiving a continuous flow LVAD as DT who were not in shock at implant, had no malignancy, and a low blood urea nitrogen (<50 mg/dL) at implant had 1- and 2-year survivals of 88 % and 80 % respectively [35]. These highly selected, low-risk patients may enjoy survival with DT LVAD that is competitive with transplant through 2 years even though they have comorbidities rendering them ineligible for transplant [36]. It remains to be seen how the ever-improving outcomes with LVADs will influence the listing criteria for heart transplant or alter allocation schemes for scarce donor organs. Decisions about the triage of patients to MCS, transplant, or MCS before transplant will face increasing scrutiny amidst a health

care environment ever more focused on cost-effective care delivery.

Upcoming Insights from INTERMACS

Now entering its second contractual period with the NHLBI, funding for INTERMACS is gradually evolving away from government support with increasing support from implanting hospitals and industry partners. The risk factors for patient morbidity and mortality identified by INTERMACS will continue to evolve as both devices and candidate selection continues to expand into "less sick" advanced HF patients. Specific attention will be directed toward better understanding right heart failure, the impact of age and frailty on outcomes, as well as benefits beyond survival alone.

Right Heart Failure

Right ventricular (RV) failure after LVAD implant confers an estimated six-fold increase in risk of death and is a major contributing factor in prolonged hospitalization [37]. Accurate assessment of RV function is required before LVAD, particularly when transplant is not a viable option, given that RV failure often persists after LVAD placement and biventricular support is not yet approved for DT [38]. Multiple RV clinical risk scores have been developed to anticipate RV failure, though none was developed in the continuous flow era and none in a DT cohort [37, 39, 40]. Since the right heart is central to all decisions about LVAD therapy, INTERMACS has established an RV Failure Working Group to develop a consensus definition of early and late right-sided HF after mechanical support in order to facilitate better event tracking between centers and pump platforms.

Frailty and LVAD Therapy

With improving outcomes in continuous flow pumps, expanded LVAD is anticipated in elderly patients as DT. Outcomes in highly selected LVAD recipients over the age of 70 have been shown to be comparable to younger patients in one single-center study [41]. However, an increase of age from 70 to 80 years was associated with an increased early post-VAD mortality risk in INTERMACS (HR 1.54, $P<0.0001$) [9••]. Nearly 75 % of patients with HF are now older than 65 years and many have significant co-morbid conditions, which may or may not be improved with LVAD therapy [36]. Frailty has been defined as the aggregation of subclinical physiological insults that results in a heightened vulnerability in the face of stress and has been called a new geriatric vital sign [42, 43]. Identifying the degree of frailty before LVAD implantation may have important implications for post-operative complications, long-term health status, and overall survival. Several methods for quantifying frailty have been developed and validated in the cardiac literature, including gait speed and grip strength [44–46]. INTERMACS will begin to collect information on frailty at the time of implant to better inform decisions about appropriate selection of older recipients for LVAD implantation.

Quality of Life

The advent of small, more durable continuous flow pumps has broadened the horizon of mechanical support to years rather than months of living with a device, particularly now that sustainable DT options are in widespread use. As a consequence, the impact of LVAD on health related quality of life and functional capacity have never been more important to consider [47]. INTERMACS has established recommendations on how best to assess longitudinally these dimensions in patients undergoing evaluation for MCS and after device therapy [48•]. Patient-centered decision making in twenty-first century medicine will include full disclosure of anticipated risks and benefits of device therapy [49]. A better understanding of how a VAD will impact quality of life and functioning will allow more appropriate candidate selection and will foster the communication of reasonable expectations for device recipients and their families.

MedaMACS

Integral to the original intent of INTERMACS was comparison to ambulatory patients living with advanced HF who are not currently receiving MCS. The lack of information on outcomes with continued medical therapy has limited the ability to define and advance indications into the "less sick". The progressively better outcomes with continuous flow LVADs documented in INTERMACS should attract ambulatory patients not yet dependent on inotropes, who currently comprise only 20 % of device recipients [9••]. The development of a contemporary parallel population of ambulatory HF patients is necessary to meet the INTERMACS goals of refining patient selection for device therapy and guiding clinical trial development for new indications and/or devices. Survival on optimal contemporary medical therapy must be defined, as well as outcomes beyond survival alone, measured in terms of quality of life, functioning and satisfaction with the chosen strategy of care. These needs will be addressed in MedaMACS (Table 2). MedaMACS will characterize patients who are not receiving LVAD currently for various reasons, including relative contra-indications, their own preferences, or their characterization as "less sick" either by perception or objective criteria.

MedaMACS will be housed with INTERMACS at the University of Alabama Birmingham. MedaMACS is a

Table 2 The MedaMACS mission

• Map terrain of contemporary medical therapy for advanced heart failure
• Identify ambulatory patients for current MCS devices
• Support Institute of Medicine mandate for patient-centered care and shared decision making
• Design integrated endpoints that move beyond survival alone
• Define a broader context for next generation of MCS trials and future devices

prospective, observational study of systolic HF patients with INTERMACS profiles 4–7 who are neither inotrope dependent nor listed for cardiac transplantation. Target enrollment will be 300 patients at 12 certified DT VAD centers in the United States with comprehensive two-year follow-up. In relation to characteristics at baseline and over time, MedaMACS will provide information on timed endpoints of VAD, transplant or death. In addition, there will be determination of adverse events such as stroke and hospitalization, for comparison to those experienced after VAD. Of equal weight will be determination of functional capacity, health related quality of life, frailty, and satisfaction with therapy. For many ambulatory patients with chronic HF, the magnitude and predictability of expected improvement in functional status with a VAD will likely influence their VAD decisions more than the margin of survival benefit.

MedaMACS will provide important context for this next wave of device studies in "less sick" advanced HF. The NHLBI has sponsored the Randomized Evaluation of VAD Intervention before Inotrope Therapy (REVIVE-IT) trial to study NYHA III patients ineligible for transplant [50]. In addition, the industry sponsored ROADMAP trial (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure) will be a prospective, non-randomized observational study of ambulatory patients with NYHA III/IV symptoms not dependent on inotropes [51]. Together with REVIVE-IT and ROADMAP, the MedaMACS program will provide data from which to refine selection for MCS from the ambulatory HF population within which the greatest benefit of mechanical support is anticipated.

The feasibility of the MedaMACS approach has been validated in a screening pilot study, which completed enrollment of 168 patients at ten VAD centers in 2010–11 using similar enrollment criteria. Data from the MedaMACS screening pilot confirmed there may be a cohort of patients

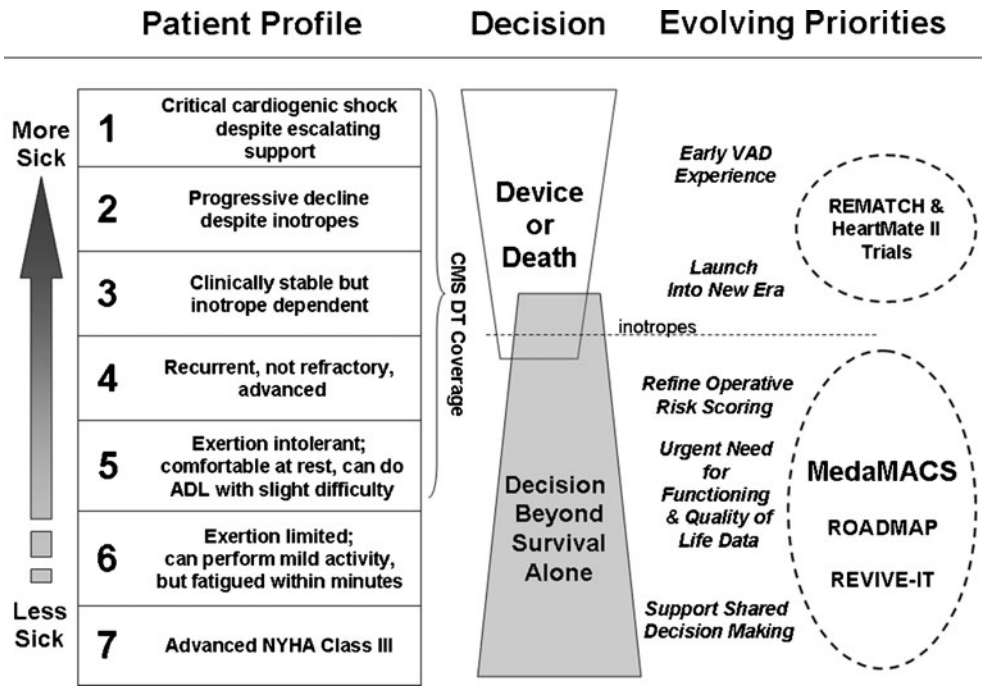

Fig. 1 Patient profiles and priorities for mechanical support in advanced heart failure: INTERMACS profiles integrate the severity and tempo of heart failure as a guide to outcomes after mechanical support. Center of Medicare and Medicaid (CMS) services current supports destination therapy (DT) coverage for patients on inotropes or those with severely reduced exercise capacity (profiles 1–5). Decisions surrounding mechanical support differ according to the level of illness in the device recipient. Patients not facing imminent death may place greater emphasis on the device's impact on their functional capacity and quality of life. Priorities for both decision-making and research have evolved as use of ventricular assist devices (VADs) has expanded into the less sick patient profiles. MedaMACS will provide important context for the next wave of device studies in INTERMACS profiles 4–7

followed at DT centers who may benefit from device therapy but who are not under current consideration for mechanical support [10]. Among medically managed ambulatory advanced HF patients, enthusiasm for considering LVAD therapy increased with lower INTERMACS profile, further validating these profiles as a marker of disease burden [52]. Early outcomes in the screening pilot after enrollment revealed one of three participants died or underwent VAD or transplant by 6 months after enrollment, highlighting the high failure rate of a medical management strategy in this population [12]. With a team of investigators and centers already established from the screening pilot, the MedaMACS study will begin enrollment in early 2013.

Conclusion

As LVAD therapy has relaunched into the continuous flow era, advances in device engineering and candidate selection have translated into dramatic improvements in outcomes, even as expanded use has generated new challenges. Together INTERMACS and MedaMACS are positioned to shape the discussion about how best to triage patients for advanced HF therapies (Fig. 1). As mechanical support moves into the less sick patient profiles, decision making will be more influenced by factors beyond survival alone. There is an urgent need for functional and quality of life data in patients limited with advanced HF both before the decision to proceed with MCS and after therapy. There will be iterative recalculation of the benefit and risk of VAD operation versus ongoing medical therapy as management strategies evolve. The synergy between INTERMACS and MedaMACS will support the new era of shared decision-making surrounding mechanical support for advanced HF.

Compliance with Ethics Guidelines

Conflict of Interest Garrick C. Stewart and Lynne W. Stevenson declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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