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EDITORIAL COMMENT

Learning From Our Predictions

The HeartMate Risk Score in INTERMACS*

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After more than 20,000 left ventricular assist device (LVAD) implantations in the United States, mechanical support devices have forever changed the epidemiology of advanced heart failure (HF). Expanded use has triggered greater scrutiny of patient selection for this expensive surgical therapy. The INTERMACS (Interagency Registry of Mechanically Assisted Circulatory Support) began mapping evolving patterns of patient selection in 2006, tracking the rapid adoption of continuous flow devices and their expanded use as destination therapy. A cornerstone accomplishment of this national registry was the development of novel patient profiles—from profile 1 (critical cardiogenic shock) to profile 7 (ambulatory advanced HF with New York Heart Association class III symptoms)—to provide a shorthand for describing the spectrum of disease within advanced HF (1). The INTERMACS registry revealed early on that patients implanted in profile 1 were at higher risk for mortality after implantation relative to less sick patient profiles. Before 2010, 29% of LVAD recipients were in profile 1, but since 2012, that proportion has diminished to only 15%, reflecting both the wider use of devices in less sick profiles and a reluctance to implant a durable device in the crash-and-burn setting (2). Although not originally intended to be a risk stratification tool, the INTERMACS profiles have shaped the discussion of candidate selection since their inception.

A vigorous debate is ongoing about the optimal timing of LVAD implantation and candidate risk stratification within the framework of these INTERMACS profiles. Fortunately, as the population of continuous flow LVAD recipients has grown, so has the statistical power to model post-implantation risk. In 2013, the HeartMate Risk Score (HMRS) was developed to estimate 90-day mortality following HeartMate II using pre-implantation data from the pivotal clinical trials. The HMRS has 5 simple, readily available variables: age, international normalized ratio, albumin, creatinine, and implantation center volume. These components capture frailty (advanced age), inflammation/malnutrition (low albumin), right heart failure (high international normalized ratio), and cardiorenal syndrome (elevated creatinine), each a proven risk marker for both heart failure and cardiac surgery. The HMRS, which is calculated as a continuous variable, can be used to stratify patients into low-, intermediate-, and high-risk groups, which demonstrated a 7-fold 90-day mortality risk difference between low- (4%) and high-risk (29%) groups in the derivation cohort (3). Yet since the initial HMRS publication, there have been conflicting reports on the utility of this model in real-world practice, with single-center reports alternatively endorsing or discouraging use. Moreover, the HMRS was derived in axial flow pump recipients and has not been robustly validated in the centrifugal flow HeartWare LVAD (Framingham, Massachusetts) now in widespread use under the bridge to transplantation indication. Uncertainty remains about how much additional information HMRS adds to simple INTERMACS profiling and how such risk modeling should shape conversations with patients and their families.

The study by Adamo et al. (4) in this issue of *JACC: Heart Failure* is a timely contribution to the literature of risk modeling in patients undergoing LVAD support. The study cohort consisted of 10,847 continuous flow LVAD recipients who received implants between 2006 and 2015 and were registered in INTERMACS, a

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prospective observational registry of approved mechanical circulatory support devices in the United States. Each LVAD recipient had an HMRS retrospectively calculated based on available pre-implantation data. The primary outcome was the association between HMRS risk group (low, intermediate, and high) and post-LVAD mortality at 90 days, 1 year, and 2 years, with a pre-specified analysis stratified by INTERMACS profiles 1, 2, 3, and 4 to 7. The HMRS had modest discrimination for mortality in this large real-world cohort of LVAD recipients (C-statistic: 0.62 for 90-day mortality; 0.60 for 2-year mortality). Patients in the high-risk HMRS group had a nearly 3-fold increased 90-day mortality compared with the low-risk group and roughly 2-fold increased 2-year mortality risk, an attenuated discrimination compared with clinical trial patients.

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The HMRS had similar performance characteristics across INTERMACS profile groups and provided additive risk stratification beyond patient profile alone, most especially for early post-implantation mortality. These findings confirm and extend the previous single-center report by Adamo et al. (5) showing that HMRS can risk stratify even the sickest INTERMACS profile 1 patients. When HMRS was added to INTERMACS profile, there was modest net reclassification, mostly from identifying patients at lower risk of mortality than might be explained by INTERMACS profile alone. The low-risk groups in sicker INTERMACS patient profiles were identified as having a similar mortality as the high-risk groups in less sick INTERMACS profiles, highlighting the spectrum of risk present within each patient profile. INTERMACS profiles are more appropriate as descriptors of HF disease burden and trajectory than as a prediction tool for post-LVAD survival. The majority of patients in this analysis received axial flow pumps (88%), but the remaining cohort of centrifugal pump recipients is the largest yet studied for evaluating HMRS performance in the HeartWare LVAD. There was no apparent difference in the discriminative power of the HMRS between axial and centrifugal flow pumps. HMRS can refine risk stratification within INTERMACS profiles and can be applied to the HeartWare centrifugal device.

Several limitations of these data should be taken into account as we incorporate these findings into decision making about LVAD candidacy. All risk scores were assigned retrospectively in LVAD recipients, a highly selected group of patients compared with the general advanced HF population. Performance of HMRS was modest, even in predicting past events. Although enthusiasm for implantation of a durable LVAD into profile 1 patients has waned since the earlier years of mechanical support, critically ill candidates stand to have the greatest absolute survival benefit with LVAD compared with the alternative of medical therapy regardless of HMRS risk grouping. Once the phase of perioperative risk and early end-organ dysfunction passes, there appears to be no additional late hazard conferred by either pre-implantation INTERMACS profile or HMRS group. Contemporary profile 1 and 2 recipients are managed differently now than they were earlier in the registry experience, with many receiving temporary circulatory support to stabilize end-organ function prior to durable LVAD, the frequency of which was not reported here. These data elide shifts in clinical practice driven by the evolving patient selection patterns and outcomes registered by INTERMACS.

How can we better operationalize risk models to inform conversations with our patients and promote shared decision making? Real or perceived decisions involve choices between alternatives. Risk models for survival with mechanical support should be juxtaposed with those for a medical prognosis with advanced HF. Although survival has understandably been the outcome of primary interest to these models, most patients with HF report that quality of life is at least as important to them when considering an LVAD (6). A model incorporating survival with good quality of life may be more relevant to conversations with our HF patients who hope to live better as well as longer. Combined endpoints will be particularly relevant for LVAD recipients in the ambulatory INTERMACS profiles 5 to 7 who may anticipate a similar survival on medical and device therapy. Fieldwide, we all must strive to understand better how to communicate effectively to our patients the risks, benefits, and genuine uncertainties confronting the choice to receive an LVAD, using risk scores to tailor our message to an individual patient.

In rapidly evolving field of mechanical support, risk modeling for purposes of patient selection and recipient education is in a constant state of refinement. Risk models will never replace clinical judgment, but they can reveal and enrich its wisdom. Ultimately, a model is only as valuable as its ability to discriminate between high- and low-risk patients and in this large real-world cohort, HMRS had only modest discriminative power. Newer, more sophisticated risk models are now under construction using Bayesian network-based methods that incorporate modern machine learning algorithms. A recent report by Loghmanpour et al. (7) confirmed that the

network model from the Cardiac Outcomes Risk Assessment project had superior performance in predicting survival compared with HMRS in the INTERMACS registry. Next-generation network models have the ability to learn from previous probability and account for relationships between variables, although they will require many more input variables. Now that decision algorithms can be embedded within electronic health records, we must embrace complexity to provide clearer answers for our patients. From so simple a beginning, endless risk models have been, and are being, evolved (8).

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