Adverse events in contemporary continuous-flow left ventricular assist devices: A multi-institutional comparison shows significant differences

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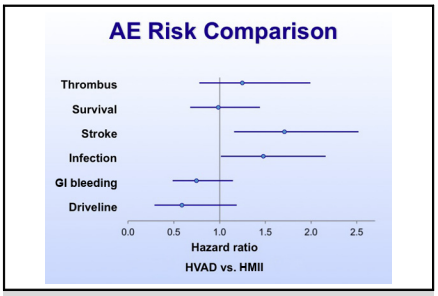
ABSTRACT

Objectives: We review differences in the incidence and timing of adverse events in patients implanted with continuous-flow left ventricular assist devices (LVADs), using the Mechanical Circulatory Support Research Network registry.

Methods: From May 2004 to September 2014, a total of 734 patients (591 men; median age: 59 years) underwent primary continuous-flow LVAD implantation at our institutions. Patients implanted with the HeartMate II (HMII) (560 [76%] patients), compared with the HeartWare ventricular assist device (HVAD; 174 [24%]) were more often receiving destination therapy (47% vs 20%; $P < .01$), had a lower preoperative creatinine level (1.2 vs 1.3; $P = .01$), and had less median preoperative right ventricular dysfunction (mild vs moderate; $P < .01$). Ischemic etiology, prior sternotomy, and median INTERMACS profile were similar.

Results: Overall mortality was 54 of 734 (7.4%); 41 of 560 (7.3%) in the HMII group, and 13 of 174 (7.5%) in the HVAD group ($P = .95$). Follow-up was available in 100% of early survivors for a median of 1 year (max: 10 years) and a total of 1120 patient-years of support (HMII: 940 patient-years [median: 1.1 years, max: 5.3 years] and HVAD: 180 patient-years [median: 0.6 year, max: 10.4 years]). On multivariable analysis, GI bleeding ($P = .63$), any infection ($P = .32$), driveline infection ($P = .10$), and pump thrombus ($P = .64$) were similar between devices while HeartWare HVAD was associated with higher risk of stroke (HR: 1.8, [1.25, 2.5], $P = .003$).

Conclusions: In this pooled analysis, a trend was found for higher incidence of percutaneous driveline infections in patients treated with the HMII; a higher incidence of stroke and time-related cumulative risk of any infection and stroke was found in patients treated with the HVAD, which was independently associated with higher stroke risk. (J Thorac Cardiovasc Surg 2016;151:177-89)



Adverse event risk for the HVAD versus the HMII LVADs.

Central Message

Patients treated with the HVAD, versus HMII, had a higher incidence of stroke and time-related cumulative risk of any infection and stroke.

Perspective

Very few large, multicenter comparisons have been done between contemporary axial- and centrifugal-flow left ventricular assist devices. Understanding these differences can substantially enhance preoperative counseling, as well as postoperative monitoring, of these patients.

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The largest analysis to date for patients undergoing implantation of a left ventricular assist device (LVAD) approved by the Food and Drug Administration was summarized in the sixth annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS); it presents an 8-year enrollment of >10,000 patients.[1] The accrual rate noted in this report now exceeds 2000 patients per year. Despite the large amounts of pooled data for these patients, from both the INTERMACS registry and multicenter clinical trials and postapproval analyses, very few direct comparisons of second- and third-generation LVADs have been done. The reports include a comparison of the

Abbreviations and Acronyms

CI	= confidence interval
GI	= gastrointestinal
HMII	= HeartMate II (LVAD)
HR	= hazard ratio
HVAD	= HeartWare Ventricular Assist Device (LVAD)
INR	= international normalized ratio
INTERMACS	= Interagency Registry for Mechanically Assisted Circulatory Support
LVAD	= left ventricular assist device

third-generation HeartWare Ventricular Assist System (HVAD; HeartWare Inc, Framingham, Mass) against a control group of commercially available devices from the INTERMACS registry,[2] a single-institution experience comparing patient outcomes for the HeartMate II (HMII; Thoratec Corporation, Pleasanton, Calif) and the HVAD,[3] and the preliminary[4] and full set[5] of data from the Endurance randomized, controlled clinical trial. Aside from these reports, very few data are available from specific comparisons of these devices.

Because very few reports are available from large, multicenter, collaborative efforts analyzing contemporary outcomes in a real-world setting, we sought to evaluate outcomes in our large cohort with an "all-comers" strategy for patients implanted with a continuous-flow LVAD. We report differences in preoperative clinical characteristics, operative procedures, and early and late outcomes, including overall survival, gastrointestinal (GI) bleeding, infection, percutaneous driveline infection, stroke, and pump thrombus. We performed a multivariable analysis, to identify independent predictors of each late outcome, and specifically device type, to detect potential independent associations with late outcomes.

METHODS

Patients

The data collection and analysis were performed after informed patient consent was obtained and the study had been approved by the University of Michigan, Mayo Clinic College of Medicine, and Vanderbilt Heart and Vascular Institute Institutional Review Board. Between May 2004 and September 2014, a total of 734 patients underwent primary continuous-flow LVAD at the centers that comprise the Mechanical Circulatory Support Research Network (University of Michigan Health System, Mayo Clinic College of Medicine, and Vanderbilt Heart and Vascular Institute). The median age at the time of operation for the entire cohort was 59 years (range: 18-82 years); 591 (80%) were men. Devices implanted include the HMII in 560 (76%), and the HVAD in 174 (24%). Stratification by device type revealed several significant differences in preoperative clinical characteristics (Table 1).

In general, for all institutions, lactate dehydrogenase is monitored weekly for the first month, monthly thereafter to the 6-month point, and then every 6 months. International normalized ratio (INR) values are closely monitored by institutional anticoagulation programs, and patients are routinely bridged with unfractionated intravenous heparin if INR <2.0. All patients with the HVAD were maintained on 325 mg of aspirin. Dipyridamole is used almost routinely by the University of Michigan before therapeutic INR, and selectively by the other institutions. Plavix was utilized on an individual basis if pump thrombus or hemolysis was observed; it is not used routinely, especially in bridge-to-transplant patients, as this would pose a greater bleeding risk at transplant. We have introduced use of bridging with low–molecular weight heparin in stable outpatients if the INR falls to <2.0 and remains >1.7, to avoid readmission.

All adverse events were defined according to the standard INTERMACS definition used during the time period of implantation. This cohort represents patients receiving continuous-flow LVAD implantation during various eras that span several important clinical trials, including the HeartMate II DT (destination therapy) trial, the HeartWare BTT (bridge to transplant) trial (ADVANCE), and the HeartWare DT (destination therapy) trial (ENDURANCE I). A segment of this population was implanted in a commercial setting, after HMII destination therapy approval in 2009, and HeartWare bridge to transplant approval in 2012.

Statistical Analysis

Demographic and other patient-related data were obtained from the University of Michigan, Mayo Clinic College of Medicine, and the Vanderbilt Heart and Vascular Institute medical record, along with our prospectively collected clinical databases. Follow-up information was obtained from subsequent clinic visits and written correspondence from local physicians. Data were expressed as either mean ± SE of the mean, for normally distributed data, or median with range for non-normally distributed data. Normality of continuous variables was assessed using the Shapiro-Wilk test. Mann-Whitney U and Wilcoxon-rank-sum were both used to compare significantly skewed continuous data.

Data between 2 groups were compared using χ^2 analysis for continuous and dichotomous variables, respectively. A backward, stepwise Cox regression analysis was used to identify perioperative variables that independently affected outcomes. Variables significant in the univariate analysis were utilized during stepwise selection to create the final multivariable model.

Variables included in the univariate analysis included the following: device type (HMII, HVAD); age at implant; gender; implanting institution; device indication (bridge, destination); heart failure etiology (dilated, ischemic); preoperative atrial fibrillation; diabetes; hypertension; total bilirubin; creatinine; hemoglobin; INTERMACS profile; preoperative inotropes; preoperative intra-aortic balloon pump; preoperative tricuspid regurgitation grade; preoperative right ventricular dysfunction; redo sternotomy; tricuspid valve surgery; aortic valve surgery; and cardiopulmonary bypass time. In addition, for pump thrombus and stroke, the eras of pre-August 2011 and post-August 2011 were entered as variables for analysis.

Kaplan-Meier survival analysis was used to evaluate time-related outcomes and create plots, which were subsequently compared using the log-rank test. Early operative mortality was defined as death within 30 days of operation, or at any time during the index hospitalization. We employed pairwise deletion to impute missing data.

RESULTS

Operative Data

All patients underwent primary continuous-flow LVAD implantation at our respective institutions. Preoperative clinical characteristics differed when stratified by device type (Table 2); significantly more patients underwent tricuspid valve surgery in the HMII cohort (n = 207; 38%) compared with the HVAD group (n = 34; 21%).

Early Outcomes

Overall mortality was 54 of 734 (7.4%); 41 of 560 (7.3%) in the HMII group; and 13 of 174 (7.5%) in the