Improved Outcomes for Women on the Heart Transplant Wait List in the Modern Era

ALANNA A. MORRIS, MD,[1,2] ROBERT T. COLE, MD,[1] S. RAJA LASKAR, MD,[1] ANDREAS KALOGEROPOULOS, MD, PhD,[1] J. DAVID VEGA, MD,[1,2] ANDREW SMITH, MD,[1] AND JAVED BUTLER, MD, MPH[3]

Atlanta, Georgia; and Stony Brook, New York

ABSTRACT

Background: Whether the routine use of continuous-flow left ventricular assist devices (LVAD) has affected gender differences in outcomes for patients listed for heart transplantation (HT) is unclear.
Methods and Results: We identified 20,468 adults (25% women) listed as status 1A or 1B for HT from 2000 to 2014. Sex differences in removal from the wait list during the first 365 days due to death or deterioration was assessed with the use of Kaplan-Meier survival analysis. Patients were stratified according to listing before (era 1) or after (era 2) Food and Drug Administration approval of the Heartmate II LVAD on April 22, 2008. Freedom from death or deterioration on the wait list was higher for men than for women (70% vs 64%; $P < .001$). After adjusting for risk factors, women had a higher risk of removal from the wait list at 365 days during both era 1 (hazard ratio [HR] 1.23, 95% confidence interval [CI] 1.10−1.36; $P < .001$) and era 2 (HR 1.15, 95% CI 1.01−1.31; $P = .029$). Further adjustment for LVAD use eliminated the higher risk for women in era 2 (HR 1.14, 95% CI 0.99−1.29; $P = .053$) and not in era 1 (HR 1.22, 95% CI 1.10−1.36; $P < .001$).
Conclusions: The higher risk for death or deterioration in women waiting for HT has improved in the modern era. (*J Cardiac Fail 2015;21:555−560*)
Key Words: Sex, heart transplant, ventricular assist device.

Heart transplantation (HT) remains the best option for select patients with end-stage heart failure (HF). Over the past decade, changes to the allocation algorithm and improvements in left ventricular assist device (LVAD) technology have led to improved outcomes for patients on the HT waiting list,[1,2] with an overall reduction in wait list mortality from 16.9 to 11.6 deaths per 100 wait list years from 2001 to 2011.[2] Similarly, wait list mortality has improved among candidates with an implanted LVAD at the time of listing, declining from 102.2 to 12.9 deaths per 100 wait list years from 2001 to 2011.

The demographic characteristics of wait list candidates has changed in the past decade, with data from the Organ Procurement and Transplantation Network (OPTN) showing that the proportion of women on the wait list has increased over time.[2] Previous studies have reported conflicting data on whether women are at a higher risk for death or deterioration on the waiting list.[3−5] Sex-based disparities with higher risk for women have been reported for periprocedural morbidity and mortality,[6,7] as well as for outcomes after VAD implantation.[8] The first-generation pulsatile LVADs were limited by their considerable bulk, and could not be implanted into patients with body surface areas <1.5 m^2, making women with smaller body habitus ineligible for that therapy. With the United States Food and Drug Administration (FDA) approval of the first continuous-flow LVAD (Heartmate II; Thoratec, Pleasonton, California) in April 2008, improvements in sex-based differences in wait list outcomes might be expected, because these smaller and more durable LVADs could be implanted in women at the same rates as in men. In the present study, we sought to assess whether wait list outcomes among men and women listed for HT have been influenced by greater use of the continuous-flow LVAD.

From the [1]Division of Cardiology Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; [2]Division of Cardiology Department of Medicine, Atlanta VA Medical Center, Atlanta, Georgia and [3]Division of Cardiology Department of Medicine, Stony Brook University, Stony Brook, New York.

Manuscript received September 22, 2014; revised manuscript received January 20, 2015; revised manuscript accepted March 9, 2015.

Reprint requests: Alanna A. Morris, MD, 1462 Clifton Road Suite 528A, Atlanta, GA 30322. Tel: 404-727-4037; Fax: 404-712-0149. E-mail: aamorr3@emory.edu

Funding Sources: NIH/NHLBI 1 U10 HL110302 (Butler) and NIH/-NINR 5 P01 NR011587−03 (Butler).

All decisions regarding this manuscript were made by a guest editor.

See page 560 for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2015.03.009

Methods

Study Population

All subjects ≥18 years of age listed for HT from January 2000 to March 2014 were identified in the OPTN database, which includes deidentified data on all patients listed for HT in the United States. The Health Resources and Services Administration and the United States Department of Health and Human Services provide oversight to the activities of the OPTN contractor, the United Network of Organ Sharing (UNOS). When listed for HT, patients are designated as UNOS status 1A, 1B, or 2 based on their degree of hemodynamic compromise. UNOS status 1A includes patients requiring VAD, total artificial heart (TAH), extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), mechanical ventilation, high-dose continuous intravenous inotropes, or an exemption for critical illness, such as ventricular tachycardia or complications with mechanical circulatory support. UNOS status 1B is the next highest status, and includes patients receiving continuous intravenous inotropes as well as stable VAD patients.

Study End Point

The primary end point was removal from the wait list by 365 days after listing due to death or deterioration. The 365-day time period was chosen because >92% of patients were removed from the wait list either for transplantation or for death or deterioration by this time. The determination that a patient has clinically deteriorated and is too sick for a transplant is made by the transplant center and is not based on any set of clinical criteria defined by UNOS. Once the decision is made by the transplant center to remove the patient from the wait list, the wait list candidate and their family are informed, and this information is entered into the UNOS wait list removal database as "Candidate condition deteriorated, too sick for transplant."

Statistical Analysis

Data are presented as median (interquartile range [IQR]), or as n (%) of patients. Baseline characteristics were compared between sexes with the use of the χ^2 test for categorical and the Mann-Whitney test for continuous variables. Unadjusted survival rates were assessed by means of the Kaplan-Meier method. Multivariable Cox proportional hazards models were developed with the use of a forward selection procedure retaining variables significant at the 0.20 level based on a likelihood ratio to test for the association of female sex and the primary end point. The proportional hazards assumption was tested and verified for all risk factors by means of Schoenfeld residual correlation analysis. Two models were considered. Model 1 adjusted for the following variables: age, white race, ABO blood group, HF etiology, body mass index (BMI), estimated glomerular filtration rate (eGFR), albumin, diabetes, insurance (private, Medicaid, Medicare, other), ventilator status, inotrope use, ECMO, IABP, pulmonary capillary wedge pressure (PCWP), cardiac index (CI), volume of listing center, and presence of defibrillator. Model 2 adjusted for type of VAD (LVAD vs other VAD [RVAD, biventricular assist device (BiVAD), or TAH]).

To test the effect of era on wait list outcomes, era was added to models 1 and 2 as a binary variable using January 2000 to April 21, 2008 (era 1) as the reference group and April 22, 2008, to March 2014 (era 2) as the comparator group. We also performed a subgroup analysis on those patients who were listed for HT after April 21, 2008. Sex-era interaction terms were added to the main effect models to assess whether any improvement in wait list survival over time was modified by sex. Stratified multivariable models were developed to confirm significant sex-era interactions in the overall model. Data were analyzed with the use of SPSS statistical software version 22 (IBM, Armonk, New York).

Results

Study Population

During the study period, 21,938 patients ≥18 years of age were listed in the United States as status 1A or 1B for HT. Of these, 1,470 patients were removed from the wait list for reasons other than the end points of interest (Fig. 1) and were excluded from the current analysis. Of the remaining 20,468 patients that formed the study cohort, 5,038 (25%) were women.

Table 1 summarizes the baseline characteristics at the time of listing for HT stratified according to sex. Women were younger, more likely to have nonischemic HF etiology, and less likely to be white, overweight/obese, have diabetes, or normal renal function. Specific nonischemic HF etiologies that were more common in women included adriamycin-induced (4.6% vs 0.5%), peripartum (6.8% vs 0%), and myocarditis (1.4% vs 0.6%). Women were more likely to require mechanical ventilation, and circulatory support with intravenous inotropes or ECMO, and they were less likely to have an implantable cardioverter-defibrillator (ICD) or to be supported with an LVAD. The median number of days on the wait list was shorter for women than for men.

Wait List Outcomes

During the overall study period, 3,542 candidates were removed from the wait list for either death (n = 2,399) or being deemed to be too sick for transplantation (n = 1,143). At 365 days, freedom from death or deterioration on the wait list was higher for men than for women

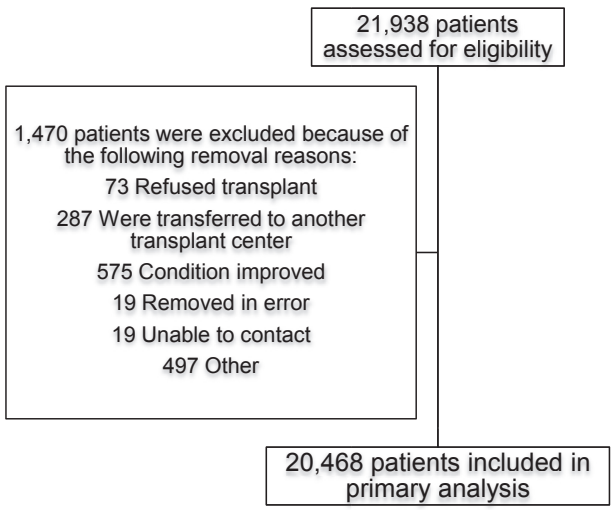

Fig. 1. Flow chart showing reasons for patient exclusion.