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Survival Benefit From Transplantation in Patients Listed for Heart Transplantation in the United States

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Objectives The aim of this study was to assess the survival benefit from heart transplantation (HT), defined as reduction in the risks for 90-day and 1-year mortality on undergoing HT close to listing, in candidates stratified by their risk for waiting list mortality.

Background Among patients listed for HT, those at higher risk for death without transplantation are also at higher risk for early post-transplantation mortality.

Methods All patients age ≥18 years listed for HT in the United States from 2007 to 2010 were analyzed. A model was developed to predict the risk for waiting list mortality within 90 days, and listed patients were stratified into 10 risk groups (deciles). All groups were followed for 1 year to assess cumulative 1-year mortality while on the waiting list. Models of 90-day and 1-year post-transplantation mortality were developed using recipient data, and these risks were estimated at listing in all listed candidates.

Results Of 10,159 patients listed for HT, 596 (5.9%) died within 90 days and 1,054 (10.4%) within 1 year without undergoing transplantation. Of 5,720 recipients of transplants with 1-year follow-up, 576 (10.1%) died within 1 year. The risk for death while on the waiting list within 90 days increased from 1.6% to 19% across the 10 risk groups. The survival benefit from HT increased progressively with higher risk for death without transplantation ($p < 0.001$ for trend), but there was no benefit in the first 6 risk groups.

Conclusions The risk for waiting list mortality varies considerably among HT candidates. Although the survival benefit of HT generally increases with increasing risk for waiting list mortality, there is no measurable benefit in many candidates at the lower end of the risk spectrum. (J Am Coll Cardiol 2014;63:1169–78) © 2014 by the American College of Cardiology Foundation

Heart transplantation (HT) is an established therapy for end-stage heart failure (1,2). Although the number of patients listed for HT in the United States continues to increase, the supply of donor hearts remains relatively unchanged (1,3). To minimize mortality in patients awaiting HT, the U.S. allocation policy has prioritized sicker candidates to receive donor hearts since the early days of transplantation (4,5). In the current 3-tier system, a patient may be listed as status 2, 1B, or 1A on the basis of criteria intended to represent increasing medical urgency. These groups are then assigned progressively higher priority during allocation (6). Because not all candidates listed at the highest urgency status (1A) share a similar risk for death while waiting, some experts have argued for a re-examination and revision of the current allocation algorithm (7,8).

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Previous studies have suggested that sicker patients among those listed for HT are also at higher risk for post-transplantation mortality (5). Although prioritizing donor hearts to candidates on the basis of transplantation urgency is justified as fairness or justice, whether it is also justifiable on the basis of higher survival benefit to such patients is unknown (9,10). A better understanding of the relationship of the survival benefit from HT with increasing risk for death on the

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Abbreviations and Acronyms

HT = heart transplantation

LVAD = left ventricular assist device

OPTN = Organ Procurement and Transplantation Network

UNOS = United Network for Organ Sharing

waiting list will be valuable not only to the physicians caring for patients with heart failure but also to the allocation experts responsible for refining the heart allocation algorithm.

We hypothesized that the survival benefit from HT estimated at the time of listing will be higher in patients at higher risk for death while on the waiting list. The specific objectives of this study were: 1) to risk-stratify patients listed for HT on the basis of their risk for death without HT within 90 days of listing; and 2) to quantify the survival benefit of HT across risk strata of waiting list mortality.

Methods

Study population. We identified all patients aged ≥ 18 years in the Organ Procurement and Transplantation Network (OPTN) database listed for their first HT in the United States between January 1, 2007, and December 31, 2010. The OPTN database includes demographic and clinical information at the time of listing in all HT candidates and at the time of transplantation in all heart transplant recipients in the United States, submitted by transplantation centers. These data are supplemented with death data in patients ever listed for HT (including for patients removed from the waiting list before undergoing HT) from the Social Security Death Master File and are provided to investigators as deidentified data. The Health Resources and Services Administration of the U.S. Department of Health and Human Services provides oversight of the activities of the OPTN contractor, the United Network for Organ Sharing (UNOS). We excluded patients who were listed for heart retransplantation or multiple-organ transplantation. Post-transplantation outcomes were analyzed in study subjects who underwent HT between January 1, 2007 and March 1, 2011. This allowed us to analyze at least 1 year of post-transplantation follow-up in all HT recipients.

Study design and definitions. The primary hypothesis was that the survival benefit from HT estimated at the time of listing would be higher in patients who were at higher risk for death without HT. Survival benefit was quantified on the basis of the estimated 90-day and 1-year risks for death without HT and with HT after listing. We first developed a risk prediction model for 90-day waiting list mortality using clinical data in listed patients and used this model to stratify listed patients into 10 groups (approximate deciles) on the basis of a progressively higher risk for death. We then developed risk prediction models for 90-day and 1-year post-transplantation mortality using clinical data at transplantation in heart transplant recipients. We applied these models to all listed patients at the time of listing and estimated these risks in each of the 10 risk groups at listing. Survival benefit was quantified in each risk group as the reduction in risks for 90-day and 1-year mortality on undergoing HT close to listing.

The primary endpoints were death without HT (while listed or after removal from the list) and death after HT. Demographic and clinical variables were defined at listing to develop the model for death without HT and at transplantation to develop models for death after HT. Race or ethnicity was recorded as reported by the transplantation center and analyzed as white (non-Hispanic white), black (non-Hispanic black), Hispanic, or other. Renal function was analyzed as estimated glomerular filtration rate (ml/min/1.73 m^2) using the Modification of Diet in Renal Disease formula (11,12).

None of the subjects had any missing data for the following variables: age, sex, race or ethnicity, cardiac diagnosis, blood type, hemodynamic support (intra-aortic balloon pump, inotrope support, ventilator, type of mechanical support), medical insurance (Medicaid), UNOS listing status, dialysis, and the dates of listing, transplantation, death, or removal from the waiting list. We imputed glomerular filtration rate values for patients with missing values at listing (0.8%) or at transplantation (0.6%) using a multiple imputation technique and clinical variables at listing and transplantation, respectively.

Statistical analysis. Summary data are presented as median (25th percentile, 75th percentile) or number (percent). Waiting list outcomes in study patients were first assessed using competing outcomes analysis (13,14). Median waiting list time, overall and by listing status, was estimated using the Kaplan-Meier method. A multivariate logistic regression model for 90-day mortality without HT was developed using variables at listing retaining variables significant at the 0.10 level on the basis of a likelihood ratio test. Model discrimination was assessed using the area under the receiver-operating characteristic curve (C-statistic) and calibration using the Hosmer-Lemeshow goodness-of-fit test. The model was internally validated using a bootstrapping technique (200 random samples, 10,159 patients in each sample with replacement). The model was used to quantify the probability of death within 90 days in each listed patient by applying model variables in that patient to the model. Listed patients were stratified into 10 groups on the basis of increasing risk for 90-day mortality without HT (approximate deciles). Observed cumulative 1-year mortality without HT was assessed in each of the 10 risk groups.

We developed risk prediction models for 90-day and 1-year post-transplantation mortality in heart transplant recipients using logistic regression and variable values at transplantation. We internally validated these models using bootstrapping, as outlined previously. We used these models to quantify the probability of 90-day and 1-year post-transplantation mortality at the time of listing in each listed patient by applying variable values at listing to the model. The survival benefit from HT at 90 days was calculated by subtracting the risk for 90-day post-transplantation mortality from the risk for 90-day mortality without HT in each risk group. Survival benefit at 1-year was calculated by subtracting the risk for