Validation of Destination Therapy Risk Score in Recipients of Left-Ventricular Assist Devices (LVAD) at a Single Center

A. Study Purpose and Rationale

It is estimated that 250-500,000 patients in the United States, and approximately 2.2 million worldwide, are currently in the terminal phase of heart failure and are refractory to maximal medical therapy[1] (American Heart Association. Heart Disease and Stroke Statistics-2004 Update. Dallas, Texas: American Heart Association; 2003.) Heart transplantation has provided the greatest survival benefit, but because of limited resources and patient-related factors rendering them ineligible for heart transplantation, many end-stage heart failure patients had been left with few treatment options. The use of left ventricular assist devices (LVADs) in patients with end-stage heart failure as a permanent alternative to heart transplantation, or destination therapy (DT), was first investigated in the landmark Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure (REMATCH) trial[2] (Rose EA, Gelijns AC, Moskowitz AG et al. for the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med. 2001;345:1435-1443.) The REMATCH group demonstrated a reduction of 48 percent in the risk of death from any cause in the group that received an LVAD as compared with the medical-therapy group (RR 0.52; 95% CI, 0.34-0.78; P=0.001). The investigators concluded that the use of an LVAD in patients with advanced heart failure resulted in a clinically meaningful survival benefit and an improved quality of life. However, the first 90 days after implantation of an LVAD is plagued with adverse events, resulting in a 28 percent risk of infection, a 42 percent risk of bleeding within the first 6 months, and high peri-operative mortality (REMATCH).

In 2007, Lietz et al. studied the outcomes of DT in 280 advanced heart failure patients who underwent LVAD implantation after completion of the REMATCH trial[3] (Lietz K, Long JW, Abdalla GK et al. Outcomes of left ventricular assist device implantation as destination therapy in the post REMATCH era. Circulation. 2007;116:497-505). The goal of the study was to identify preoperative predictors of in-hospital mortality after pump implantation, which would help physicians to prospectively select DT candidates and to improve long-term success of LVAD therapy. Based on the results of this study, a preoperative risk score for in-hospital mortality after LVAD implantation was established (Destination Therapy Risk Score or DTRS). The parameters determined to predict 90-day in-hospital mortality are: platelet count $\leq$ 148 x 10^3/ μL, serum albumin < 3.3 g/dL, international normilization ratio >1.1, vasodilator therapy at time of implantation, mean pulmonary artery pressure $\leq$25.3 mm Hg, aspartate aminotransferase >45 U/dl, hematocrit $\leq$34%, blood urea nitrogen >51 U/dL, and lack of intravenous

inotropic support. Each of the 9 variables entered into the multivariable model was assigned a weighted risk score. The cumulative risk score was calculated for each patient and ranged from 0 to 27 with higher score indicating higher 90-day in-hospital mortality. Patients were divided into 4 operative risk categories based on the probability of 90-day in-hospital mortality: low (probability <0.10; n-65), medium (probability 0.01 to 0.50; n=111), high (probability 0.50 to 0.70; n=28), and very high (probability >0.70; n=18). The observed survival to hospital discharge in low, medium, high, and very high operative candidates was 87.5%, 70.5%, 26%, and 13.7%.

The goal of this study is to validate the model in heart failure patients who underwent *de novo* HeartMate (HM) LVAD implantation at the Columbia-Presbyterian Medical Center in New York between January 1, 2000 and August 13, 2008. Our hypothesis is that the DTRS will predict 90-day in-hospital mortality in our cohort of patients.

B. Study Design and Statistical Analysis

Primary outcome is 90-day in-hospital mortality. In-hospital mortality after LVAD implantation is defined as death prior to discharge from implanting center to home, hospice, or rehabilitation facility. The survival analysis will be censored at the time of hospital discharge or transplant prior to hospital discharge. The study uses a retrospective, longitudinal design. Survival estimates will be based on the Kaplan-Meier method and compared using log-rank statistics. Patient survival will be calculated from the day of LVAD implantation until death on mechanical support and will be censored at time of transplant, device reimplantation or day of the last observation. The model goodness of fit will be tested using C-statistic and the Hosmer-Lemeshow test. The results will be compared with the DTRS derivation cohort of 280 patients who underwent HeartMate I implantation as DT between November 2003 and June 2005 in the US.

Power calculations were based on results obtained from the derivation cohort. It was determined that we will need 45 in-hospital deaths in the consecutive patient sample to validate the 9-risk factors of the DTRS (5 deaths per one risk factor in the score). Based on 27% in-hospital mortality in a 222 patient cohort, our goal sample size is 169 patients.

The patient data will be obtained from the U.S. FDA-mandated Destination Therapy Registry maintained by the manufacturer of HM LVAD (Thoratec Corp. Pleasanton, California), which collected information on all DT recipients in the US and from the prospective institutional LVAD database and patient chart review at the Columbia-Presbyterian Medical Center. All study patients provided written consent to use clinical information for this analysis. In addition, 66 hospitals which participated in the DT Registry and the Columbia-Presbyterian Medical Center obtained local Institutional Review Board approval to use patient data for this analysis. All recipients of DT in the post-REMATCH era who met the

general criteria for LVAD implantation which are based largely on the criteria used for patient entry into the REMATCH trial (citation) including (1) class IV NYHA symptoms for at least 60 days despite maximized oral therapy or requirement of inotropic support as outlined by the AHA/ACC guidelines for heart failure treatment (citation); (2) left ventricular ejection fraction of $\leq$ 25%; (3) peak oxygen consumption of < 12 mg/kg/min or documented inability to wean intravenous inotropic therapy, and (4) contraindication to heart transplantation due to either age > 65 or comorbidities such as insulin-dependent diabetes mellitus with end organ damage, chronic renal failure or other morbidities will be included on our study. Exclusion criteria include recipients of other pumps than HeartMateI LVAD and patients who require short-term implantable pump support as bridge-to-bridge prior to LVAD placement.

C. Study Procedure

D. Study Drugs

E. Study Device

F. Study Questionnaires

G. Study Subjects

H. Recruitment of Subjects

I. Confidentiality of Study Data

J. Potential Conflict of Interest