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Outcomes in Patients With Symptomatic Cerebrovascular Disease Undergoing Heart Transplantation

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Objectives We sought to determine outcomes in patients with and without symptomatic cerebrovascular disease (sCVD) undergoing heart transplantation. Second, we sought to determine factors associated with stroke in the perioperative period after heart transplantation.

Background sCVD is considered a relative contraindication to heart transplantation. Despite this concern, outcomes in patients with sCVD undergoing heart transplantation have not been well defined.

Methods Data on all single-organ heart transplants performed in the United States between April 1994 and December 2006 in patients age 40 years or older were analyzed. Survival analysis was performed to examine the effect of sCVD on the combined outcome of stroke or death, stroke, death, and functional decline, adjusting for potential confounding variables over long-term follow-up. In a separate analysis, predictors of perioperative stroke during the transplant-related hospitalization were examined using multiple logistic regression.

Results There were 1,078 patients with and 16,765 patients without sCVD. The annualized rates of stroke or death (11.5% vs. 7.8%; $p < 0.001$), stroke (4% vs. 1.4%; $p < 0.001$), death (8.9% vs. 7.4%; $p < 0.001$), and functional decline (3.7% vs. 3.0%; $p = 0.002$) were higher in patients with sCVD than in patients without sCVD. In multivariable analysis, patients with sCVD were at increased risk of stroke or death (hazard ratio [HR]: 1.29; 95% confidence interval [CI]: 1.17 to 1.42), stroke (HR: 2.24; 95% CI: 2.02 to 2.87), and functional decline (HR: 1.21; 95% CI: 1.03 to 1.42) compared with those without sCVD. We did not identify a higher risk of death in patients with sCVD (HR: 1.08; 95% CI: 0.98 to 1.20), compared with those without sCVD. sCVD, ventilator use, and ventricular assist device use were the most important predictors of perioperative stroke.

Conclusions Patients with sCVD are at an increased risk of stroke and functional decline after transplantation independent of other variables, but not death, during long-term follow-up. These results should assist programs in making informed decisions in patients with sCVD who are undergoing evaluation for heart transplantation. (J Am Coll Cardiol 2011;58:1036–41) © 2011 by the American College of Cardiology Foundation

Heart transplantation is increasingly being performed in patients older than 60 years of age and in those with comorbidities (1). Cerebrovascular disease is considered a relative contraindication to heart transplantation (2,3). Data on outcomes associated with a number of pre-transplant recipient comorbidities exist, but outcomes in patients with cerebrovascular disease undergoing heart transplantation have not been evaluated (4).

Patients with symptomatic cerebrovascular disease (sCVD), defined as previous transient ischemic attack (TIA) or stroke, are at increased risk of further cerebrovascular events (5,6). Patients with a history of TIA or stroke are also at increased risk of death in the long term, with

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60% of them dying at 10 years in 1 study (7). Heart transplantation involves allocation of a scarce resource among waitlisted candidates, and the benefits of improved survival and quality of life depend on the degree of recipient comorbidities. It is therefore important to define outcomes in patients with cerebrovascular disease undergoing heart transplantation.

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We conducted a retrospective analysis of heart transplant recipients to examine the long-term risk of stroke and death, stroke, death, and functional decline, in patients with and without sCVD. In separate analysis, we examined factors associated with the risk of perioperative stroke during transplantation-related hospitalization.

Methods

This analysis was based on data on all heart transplantations performed in the United States between April 1, 1994, and December 31, 2006, obtained from the Organ Procurement and Transplant Network (OPTN), as of February 6, 2008. We restricted the analysis to all first-time, single-organ heart transplant recipients age 40 years or older. sCVD was a yes/no variable on the transplantation candidate registration form and was intended to capture patients with a previous cerebrovascular event or a TIA at registration. Additional data were available on cerebrovascular events between candidate registration and transplantation. We defined sCVD as the presence of sCVD at candidate registration or the occurrence of a cerebrovascular event between candidate registration and transplantation. Of the 20,227 eligible patients, 2,384 were excluded due to missing data on sCVD at candidate registration or missing data on cerebrovascular event between candidate registration and transplantation. Data on stroke during the transplant-related hospitalization and during follow-up were collected at discharge and at follow-up visits at 6 months, 1 year, and yearly thereafter. Data on patients' functional capacity were collected at transplant recipient registration and at follow-up visits as described previously. For patients who died during follow-up, the date of death as recorded by the OPTN was used. For patients who did not have a date of death recorded by the OPTN but a date of death was available from the social security death masterfile, included in the dataset from the OPTN, this date was used. In the analysis examining factors associated with perioperative stroke, patients without data on sCVD were included, but those without information on perioperative stroke were excluded. Of 20,227 patients, 1,092 were excluded due to missing data on perioperative stroke. Perioperative stroke was defined as stroke occurring anytime during the transplantation-related hospitalization.

One of 2 different scales for functional status was used for a given patient during the period under study in the OPTN database. These scales are shown in Online Table S1. We dichotomized functional status as either good or reduced for the purpose of this study. A functional status of "performs activities of daily living with no assistance" or higher or "80%, normal activity with effort: some symptoms of disease" or higher on these scales was arbitrarily defined as good functional status. A functional status of "performs activities of daily living with some assistance" or lower or "70%, cares for self: unable to carry on normal activity or active work" or lower was defined as reduced functional status. A transition from good functional status to reduced functional status as defined was considered functional decline for time-to-event analysis. Because patients could have a temporary decline in functional status, the definition of functional decline required that patients continue to have reduced functional status as defined for the rest of follow-up, excluding those with return to good functional status from this definition of functional decline. Patients who had reduced or missing functional status at transplantation and continued to have reduced or missing functional status throughout follow-up were excluded.

Abbreviations and Acronyms

AFT = accelerated failure time
CI = confidence interval
CM = cardiomyopathy
COPD = chronic obstructive pulmonary disease
HR = hazard ratio
HTN = hypertension
OPTN = Organ Procurement and Transplant Network
PH = proportional hazard
sCVD = symptomatic cerebrovascular disease
TIA = transient ischemic attack
VAD = ventricular assist device

Unadjusted annualized event rates (expressed as percent per year) of combined outcome of stroke or death, stroke, death, and functional decline in both groups were calculated by dividing the number of events by person-years of follow-up multiplied by 100. Unadjusted cumulative incidence of outcomes at various time points were obtained by the Kaplan-Meier product-limit method. For stroke or functional decline that occurred between 2 follow-up visits, this was assumed to have occurred at the midpoint of the interval. Equality of survival curves was tested using log-rank test.

Effect of sCVD on the risk of combined outcome of stroke or death, stroke, death, and functional decline during follow-up was examined using Weibull's accelerated failure time (AFT) model. Weibull's AFT model was chosen for its ability to handle interval censored data. Stroke and functional status were interval censored in our data, being collected only at follow-up visits. The models were adjusted for donor and recipient age, sex combination, race, etiology of cardiomyopathy (ischemic vs. nonischemic), drug-treated hypertension (HTN), diabetes, drug-treated chronic obstructive pulmonary disease (COPD), dialysis status, waitlist status, ventilator use, ventricular assist device (VAD) use, creatinine, bilirubin, ischemia time, and year of transplantation. Missing values of covariates were replaced by their median or most common value for continuous and categorical variables, respectively. Additionally, a Cox proportional hazards (PHs) model was created for the outcome of death and results compared with those of the Weibull AFT model.

A multiple logistic regression model was used to examine factors associated with perioperative stroke. The model was