Optimal Medical Therapy Is Superior to Transplantation for the Treatment of Class I, II, and III Heart Failure
A Decision Analytic Approach
R.S. Freudenberger, MD; J. Kim, MD; I. Tawfik, MD; F.A. Sonnenberg, MD

Background—The survival benefit of heart transplantation (HT) compared with optimal medical therapy (OMT) has never been tested.

Methods and Results—We created a decision analytic model that simulates a randomized clinical trial of OMT versus HT for each New York Heart Association (NYHA) class. The simulation calculates average life expectancy. The following assumptions were made for OMT annual mortality: class I no excess mortality from HF; class II and III based on MERIT-HF are 5.3% and 8.1%. Class IV is 12.8%, based on COPERNICUS. HT mortality rates were based on survival curves for HT 1982 to 2001. For classes I, II, and III, OMT demonstrated a life expectancy gain of 113 months (232±2.2 versus 119±2.1), 38 months (152±2.1 versus 114±2.1), and 6 months (117±1.8 versus 111±2.2), respectively, over HT. Class IV favored HT with a life expectancy gain of 26 months (107±2.1 versus 81±1.4) over OMT. Sensitivity analysis revealed if improvement in OMT decreased mortality by 38% for class IV patients, OMT and HT would have equivalent life expectancies. If improvement in HT resulted in a 7% increase in post-HT survival, OMT and HT would be equivalent for class III patients. If improvement in HT resulted in a 30% increase in post-HT survival, OMT and HT would be equivalent for class II patients.

Conclusions—Our model predicts that currently, OMT is superior to HT for classes I, II, and III, but HT is superior for class IV. However, future advances in OMT or HT may change the relative benefits of these treatment modalities. (Circulation. 2006;114[Suppl I]:I-62–I-66.)

Key Words: decision analysis ▪ heart failure ▪ transplant

Heart failure is estimated to afflict >5 million people in the United States, with an estimated 500,000 new cases diagnosed annually.1 It is the only major cardiovascular disorder that is increasing in incidence and prevalence. Treatment of heart failure (HF) is complex. Cardiac transplantation is one approach for those with refractory symptoms, but the decision to proceed with transplantation is a challenging and often difficult process. The limited donor pool, taken together with the advances in medical therapy for HF, necessitates a critical approach in deciding whether transplantation is the most appropriate treatment.2

To date, no prospective randomized study comparing heart transplantation (HT) to optimal medical therapy (OMT) has been reported. Recent studies in which beta-blockers were added to standard treatment of HF imply that the survival rate for at least some people with advanced heart failure may exceed 95% per year. Historical data reports that the 1-year survival rate after cardiac transplantation is only 85%. Furthermore, physicians must account for long waiting times and a 20% risk of death while waiting for a heart to become available.

Decision analytic models have been used to answer important clinical decisions in medicine.3 A Markov model simulates a hypothetical cohort of patients making transitions among various health states. We created a decision analytic model that simulates a randomized clinical trial of medical therapy versus HT. The simulation ultimately calculates the average life expectancy of the cohort and is applicable to present day therapeutic realities. Furthermore, we examined which treatment modality is preferable for each New York Heart Association (NYHA) functional class.

Methods

NYHA functional classification was used for primary disease states. Cohorts were categorized as NYHA I, II, III, and IV, because each classification or state is thought to represent different risks. We adapted a Markov model developed to assess outcomes of patients with heart failure, assigned to either medical therapy or HT (Figure 1) using Decision Maker for Windows (Pratt Medical Group and UMDNJ 2005).4 Each month, patients in this Markov tree were at risk for sudden death from cardiac causes, nonsudden death from cardiac causes, and death from noncardiac causes. We assumed that the excess mortality from cardiac disease was constant for a given...
Figure 1. The decision model. A, The root of the decision tree. Chance nodes are represented by circles; brackets indicate branches that lead to the same subtree. Rectangles represent states in which a patient begins the following cycle. The square at the left of the figure indicates the decision node with one branch for each strategy. Both strategies lead to the Markov node. Each branch of the Markov node represents a distinct health state. Patients begin in one of the heart failure states (classes I, II, III, or IV). These lead to the Medical Subtree (B). The first chance node models whether the patient dies, is hospitalized for CHF, or undergoes transplant (this probability is nonzero only for the transplant strategy). The next chance node models events occurring subsequent to transplantation including Death, transplant vasculopathy or renal failure. C, Post-transplant subtree, which represents the post-transplant events, which include death, hospitalization for acute illness including rejection, infection and “other,” and the development of CAD, malignancy, or renal failure which may occur in combination.
functional class. We also incorporated data from the US general population to account for the increase in age- and sex-specific rate of death from noncardiac causes as the cohort aged. A cohort is first assigned to a particular health state by NYHA functional class. There are 2 treatment arms that are compared in this model: OMT and HT. For OMT, individual patients are then simulated to proceed to subsequent health outcomes, including: “dead,” “hospitalized,” or “no change.” For the HT arm, individuals begin waiting for a transplant which occurs at a defined rate, based on average organ waiting times. It is assumed that patients receive OMT while awaiting HT. Mortality and hospitalization rates before transplantation are based on large-scale beta-blocker clinical trials (COMET, COPERNICUS, MERIT-HF). Rates for receiving transplantation and wait times are taken from United Network of Organ Sharing (UNOS) data. In the HT arm, individuals may proceed to several post transplant states, according to clinical disease states that may occur after HT; these are: “post-transplant well,” “CAD,” “malignancy,” “renal failure,” and “dead.” Individuals are assigned to these disease states at rates based on data from the International Society of Heart Lung Transplantation. The model allows individuals to have multiple disease states and hospitalization after transplant for acute events such as rejection and infection. Mortality rates for patients after transplant are also from the annual report of the International Society of Heart Lung Transplantation. For both treatment arms, patients progress through the Markov tree until they die. Cohorts of 10,000 patients are simulated for each functional class. For each functional class, the model then calculates the average life expectancy in months. Univariate sensitivity analyses were performed to quantify how improvements in survival for OMT or HT could make them equivalent treatments. The authors had full access to the data and take responsibility for their integrity. All authors have read and agree to the manuscript as written.

Data
Construction of the model required the following assumptions: for OMT, class I confers no excess mortality caused by HF; class II and III mortalities are based on MERIT-HF and assumed to be 5.3% and 8.1% per patient year of follow-up, respectively. Class IV annual mortality for OMT is 12.8%, based on COPERNICUS. Based on the survival values from these publications, we assume excess mortality caused by HF is constant over time. HT mortality rates were based on the actual survival curves for HT 1982 to 2001 from the International Society of Heart Lung Transplantation.

Results
For classes I, II, and III, OMT demonstrated a life expectancy gain of 113 months (232 ± 2.2 versus 119 ± 2.1), 38 months (152 ± 2.1 versus 114 ± 2.1), and 6 months (117 ± 1.8 versus 111 ± 2.2), respectively, over HT. Class IV favored HT with a life expectancy gain of 26 months (107 ± 2.1 versus 81 ± 1.4) over OMT. Univariate sensitivity analysis revealed that for the class II cohort, a 30% decrease in mortality for transplantation, and for class III a 7% decrease of mortality for transplantation would result in equivalency (Figures 2 and 3). For class IV patients, transplantation is favored for all values examined. For class IV if mortality with medical therapy decreased by 38% or more then medical therapy would be favored over transplantation.

Discussion
This article represents the first analysis of medical therapy versus heart transplantation in the modern era. Randomized studies examining the use of medical therapy versus cardiac transplantation for patients with advanced HF have not been performed and to our knowledge none is ongoing or planned. Furthermore, the impact of confounding variables such as time on the list and listing status has not been directly addressed. It is not known whether these confounding variables change the threshold NYHA Class at which cardiac transplantation offers a survival advantage. Given that heart failure is currently the single most frequent discharge diagnosis in the Medicare population in the United States this question is significant. Furthermore, as the US population ages and the number of younger patients with heart failure also continue to rise, the prevalence of the syndrome will undoubtedly increase. Whereas ongoing advances in the medical treatment of clinical HF have had a favorable impact on the long-term outlook for HF patients, many patients still deteriorate despite optimal therapy and often succumb to a progressive downhill HF course or to sudden death. A paucity of donor hearts, limited post-transplant life expectancy, mortality rates on the transplant waiting list, high
costs, and challenges of post-surgical care render transplantation a feasible option for only a small fraction of patients with HF. Stringent criteria for transplantation are necessary to select the few patients with advanced stage HF despite maximal medical treatment, who are most likely to derive a survival benefit from cardiac transplantation.

Clinicians dealing with advanced heart failure patients face this challenging decision process on an almost daily basis. Given the absence of direct research data to aid in this decision-making, the potential value of a decision analytic approach to these questions is obvious. With this approach, we can apply the latest clinical trial data and reported transplant outcome data to analyze these important questions for different clinical subsets and comparing alternative initial strategies. Furthermore, as we plan for alternative strategies understanding the sensitivity analyses are critical.

Limitations
Limitations of this analysis include the following; the values were based on data whose patient populations may not be precisely comparable. The data and studies used for the analysis were collected in different years. The particular studies chosen for these analyses represent the most robust data available for each NYHA class. It should be noted, however, that most clinical trials have strict entry criteria such as renal function and a period of relative stability before randomization, thus likely representing a relatively healthy group. Whether these data can be directly generalized to the non-study population must be considered. Nevertheless, these data are robust and represents the only survival data by NYHA classification. To make the best possible estimate of survival with current optimal medical therapy, we used survival data from cardiac resynchronization and ICD studies (CARE-HF,11 COMPANION,12 SCD-HeFT13) to represent survival with current optimal medical (non-transplant) therapy. The outcomes were virtually identical. For class II, the gain from medical therapy was 31.2 months (versus 38 months in the base case analysis) and for class III-IV the gain from HT was 25.6 months (versus 26 months for class IV in the base case analysis). In these studies, mortality with class IV alone was not reported separately because of small numbers in this group. Using the most recent registry data reported recently such as ADHERE was considered but not performed because this selects the acutely decompensated hospitalized patient that may not have been maximally or optimally treated before admission.14 Furthermore, unlike clinical trials the usage rates of proven outpatient therapies were low in patients in the ADHERE registry.

Other limitations of this analysis are that the medical outcomes were stratified by NYHA class alone rather than other variables that may be used to assess prognosis in heart failure. NYHA class was chosen as this is used most frequently and the data are most robust. Furthermore, in clinical practice, a complex set of variables are used to make decisions regarding optimal medical care and were not modeled here. Finally, the quality-of-life adjustments were based on expert opinion when not available in the literature.

Conclusions
Our model is the first model to our knowledge constructed to compare these strategies for the management of heart failure in the current era. Our model predicts the superiority of medical therapy for class I, II, and III and superiority of transplantation for the class IV cohort. We were also able to demonstrate that for class III HF a small change in outcomes would “tip the scales” toward transplantation and for the other classes large changes in outcomes would be necessary to change to change the aforementioned results.

Disclosures
None.

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doi: 10.1161/CIRCULATIONAHA.105.001412
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/1_suppl/I-62

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