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Decreasing Survival Benefit From Cardiac Transplantation for Outpatients as the Waiting List Lengthens

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Many patients are accepted for cardiac transplantation during a period of clinical instability associated with a high risk of death, even though most can be discharged home to await transplantation. As the waiting lists lengthen, priority is awarded solely on the basis of the waiting time of outpatients, who now usually undergo transplantation after they have already survived a major period of jeopardy. To determine the impact of the current waiting times and priority system on the previously expected benefit offered by transplantation, 1-year actuarial survival without transplantation was recalculated after each month without transplantation for 214 potential candidates with an ejection fraction of 0.17 ± 0.05 discharged on tailored medical therapy after evaluation. These data were compared with the 1-year survival data of 88 outpatients who underwent transplantation.

Actuarial survival after 1 year was 67% on tailored therapy compared with 88% after transplantation ($p = 0.009$). Death without transplantation was sudden in 43 of 51 patients, resulting from hemodynamic decompensation in 8. For outpatients already surviving 6 months without transplantation, actuarial survival over the next 12 months was 83% without transplantation. Thus, the expected improvement in survival after transplantation would be only 5% over the subsequent year for patients waiting 6 months, which is the waiting time for many outpatients. Such patients should be reevaluated to determine whether transplantation remains indicated during the next year.

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Many patients with heart failure are referred to transplant centers for evaluation during a period of deterioration when the mortality rate is high without transplantation, whether or not the patient is actually on a waiting list. For such patients, tailored therapy with high doses of vasodilators and diuretic drugs often allows stabilization and hospital discharge before transplantation (1,2). Because of the increasing demand for transplantation in the setting of a relatively fixed supply of donor hearts, the average waiting time for outpatients has lengthened to almost 6 months, frequently to >1 year (3). Transplantation in such patients is thus performed in a group selected by having already survived for an extended period that encompasses their greatest interval risk because the heart failure survival curve falls most steeply early after referral (4).

The current national policy awards outpatient priority solely on the basis of waiting time. For patients surviving after months on the waiting list, stabilization and clinical improvement frequently occur so that functional capacity is similar to that after transplantation (2,5). Although these survivors receive the highest outpatient priority for the limited donor hearts, the relative benefit of their late transplantation has not been determined.

The purpose of this study was to determine subsequent survival on tailored medical therapy after evaluation as a function of the length of time already survived without transplantation to contrast the expected survival benefit from late transplantation with the survival benefit expected if transplantation were performed at the time of initial listing. It was hypothesized that the difference between subsequent survival with and without transplantation would decline as the waiting time increased.

Methods

Study patients (Table 1). All patients with heart failure referred to this cardiac transplantation program since 1985 have undergone a standardized baseline evaluation, including clinical assessment, echocardiography and coronary

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Table 1. Clinical Profile of 214 Patients at the Time Referred for Transplantation

	Entire Group	Nonsurvivors	Survivors		
			All	Medical Treatment Only	Medical Treatment Until Transplantation
No. of patients	214	51	163	70	93
Age (yr)	48 ± 12	44 ± 13*	49 ± 11	50 ± 11	49 ± 12
CAD	102 (48%)	21 (41%)	81 (50%)	30 (43%)	50 (54%)
NYHA functional class	3.5 ± 0.5	3.5 ± .5	3.5 ± .6	3.5 ± 0.6	3.5 ± 0.6
Previous vasodilator therapy	149/214 (70%)	33/51 (65%)	116/163 (71%)	54/70 (77%)	62/93 (67%)
Activity limitation*	3.1 ± 0.9	3.2 ± 0.9	3.1 ± 0.9	3.0 ± 0.9	3.2 ± 0.9
Orthopnea*	2.2 ± 1.4	2.6 ± 1.3*	2.2 ± 1.4	2.2 ± 1.4	2.1 ± 1.4
Right-sided congestion*	1.5 ± 1.3	2.0 ± 1.4*	1.4 ± 1.2	1.4 ± 1.2	1.4 ± 1.2
LVEF	0.17 ± 0.05	0.17 ± 0.05	0.18 ± 0.06	0.19 ± 0.06	0.18 ± 0.05
LVEDD (mm)	72 ± 19	72 ± 17	71 ± 19	71 ± 18	71 ± 20
Serum Na (mEq/liter)	135 ± 5	134 ± 6*	136 ± 6	136 ± 6	136 ± 5

*p < 0.05 comparing survivors and nonsurvivors. †On a 0 to 4 scale designed for patients with heart failure (2). CAD = coronary artery disease; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; Na = sodium; NYHA = New York Heart Association.

arteriography and endomyocardial biopsy if indicated. Left ventricular ejection fraction is calculated from radionuclide angiography in most patients and from two-dimensional echocardiography in some patients with nonischemic cardiomyopathy. Activity limitation, orthopnea and right-sided venous congestion causing splanchnic discomfort or peripheral edema are graded on a scale of 0 to 4 specifically designed for this group of patients (2). Baseline hemodynamics are determined from the results of right heart catheterization performed while the patient is receiving all previously prescribed medical therapy.

For this study, patients evaluated between July 1985 and June 1989 were included if they were >18 years of age and had an ejection fraction ≤30% and a history of decompensation with New York Heart Association functional class III or IV symptoms and could be discharged home after acceptance as a potential cardiac transplant candidate. Patients with nonischemic cardiomyopathy of recent onset (<6 months) whose condition could be stabilized were not included because of the variable time and status of presentation (in some cases not requiring current hemodynamic measurements despite previous compromise) and the high incidence of spontaneous improvement (6). Patients were excluded if they had standard contraindications that were considered sufficient to preclude any consideration as a candidate during the next 6 months, including patients with a history of refractory noncompliance (7,8).

Of the 214 patients included, 151 were placed on the waiting list after evaluation. 28 were accepted pending resolution of minor problems such as smoking, periodontal disease or financial negotiations and 35 patients were not yet able to make the commitment to transplantation. This was a retrospective study in which patients underwent transplant evaluation, tailored medical therapy and, in some cases, transplantation as routinely performed in this institution. Consent was obtained for the standard procedures of evaluation and transplantation without separate Human Subject Committee consideration.

Study patients. If the routine right heart catheterization showed two sets of hemodynamic measurements separated by 1 h in which the cardiac index was <2.25 liters/min per m^2 or the pulmonary capillary wedge pressure was >22 mm Hg, or both, the pulmonary artery catheter was left in place and therapy was systematically tailored to achieve hemodynamic goals of pulmonary wedge pressure ≤15 mm Hg, right atrial pressure ≤8 mm Hg and systemic vascular resistance ≤1,200 dynes·s·cm^{-5}, while the systolic blood pressure was maintained at ≥80 mm Hg, as previously described (1,9–11), to minimize mitral regurgitation, maximize cardiac output and improve clinical status in this group of patients.

Therapy was begun with nitroprusside, then replaced by increasing doses of oral vasodilators titrated to achieve the same hemodynamic goals. At discharge, an angiotensin-converting enzyme inhibitor was prescribed for 108 patients and hydralazine for 93; isosorbide dinitrate was added in 140 patients. Digoxin was maintained to achieve levels of 1 to 2 ng/ml, except in patients with contraindications. No patients received investigational drugs. Those patients whose condition could be stabilized were discharged after instruction regarding a progressive walking program and a flexible diuretic regimen adjusted according to daily weight. Subsequent outpatient visits were initially made weekly, then less often as stability was demonstrated (2).

Cardiac transplantation. During the same period of time, 93 of the 214 adult patients underwent cardiac transplantation after being discharged to wait at home. There was no provision among outpatients for more compromised patients to receive transplantation first; time on the list was the only determinant for the recipient of a given blood type and body size. The surgical procedure, immunosuppression (triple-

Table 2. Hemodynamic Profiles on Previous Therapy and on Tailored Therapy

	Entire Group	Nonsurvivors	Survivors		
			All	Medical Treatment Only	Medical Treatment Until Transplantation
No. of patients	214	51	163	70	93
At referral					
MAP (mm Hg)	81 ± 17	79 ± 16	81 ± 17	82 ± 19	81 ± 16
RAP (mm Hg)	12 ± 7	14 ± 7	12 ± 7	12 ± 7	12 ± 7
PCW (mm Hg)	26 ± 10	27 ± 8	25 ± 11	25 ± 10	26 ± 10
CI (liters/min per m²)	2.0 ± 0.5	2.0 ± 0.6	2.0 ± 0.5	2.1 ± 0.6	2.0 ± 0.5
HR (beats/min)	90 ± 14	93 ± 16	91 ± 17	92 ± 16	91 ± 17
Serum creatinine (mg/dl)	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.3
Before discharge					
MAP (mm Hg)	72 ± 18	74 ± 21	73 ± 12	75 ± 11	73 ± 13
RAP (mm Hg)	6 ± 3	8 ± 4*	6 ± 4	7 ± 4	6 ± 4
PCW (mm Hg)	15 ± 7	18 ± 7*	14 ± 6	13 ± 6	15 ± 7
CI (liters/min per m²)	2.7 ± 1.3	2.6 ± 0.4	2.6 ± 0.6	2.7 ± 0.7	2.5 ± 0.5
HR (beats/min)	91 ± 14	95 ± 13	91 ± 15	92 ± 16	90 ± 14
Serum creatinine (mg/dl)	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.4

*$p < 0.01$ between survivors and nonsurvivors. CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; PCW = pulmonary capillary wedge pressure; RAP = right atrial pressure.

drug therapy instituted routinely since mid 1986) and routine surveillance biopsies were performed according to standard protocols (8). The program performance met the criteria and has received Medicare approval as a cardiac transplant center.

Statistics. Statistical analysis was performed with use of the BMDP statistical package (12). Actuarial survival curves were calculated according to the Kaplan-Meier method, with patients withdrawn from medical follow-up at the time of transplantation. Only the 88 patients remaining out of the hospital until transplantation were included in the calculation of outpatient transplantation survival. Survival curves were compared by using the Mantel-Cox statistic. Actuarial survival was recalculated for the subsequent 1 year after each month of survival without transplantation. The difference between that actuarial 1-year survival and the actuarial survival observed for outpatients who underwent transplantation was defined as the expected survival benefit for survivors on a waiting list. The 1-year survival after transplantation was considered to be 88% for outpatients undergoing transplantation, regardless of waiting time.

For purposes of comparison, operative mortality rate and actuarial 1-year survival were also calculated for 64 hospitalized patients seen during the same time period who remained in the hospital until urgent transplantation and were not included with the 214 discharged patients in the study.

Results

Initial evaluation and tailored therapy (Table 2). The initial profile of the 214 patients showed an ejection fraction of 0.17 ± 0.05. Activity limitation and orthopnea were marked. Evidence of decompensation at the time of referral was such that transplantation was considered appropriate, as described by current criteria (7). Despite previous diuretic therapy in all patients and vasodilator therapy in 70% of patients, major elevations initially present in pulmonary capillary wedge and right atrial pressures and systemic vascular resistance frequently responded to subsequent therapy tailored to approach normal hemodynamics, as previously described (1,2).

Outcome after discharge. Actuarial survival of patients discharged home on tailored therapy was 67% at 1 year without transplantation (Fig. 1). Death occurred suddenly or during sleep in 43 of the 51 patients who died after evaluation and discharge. The average time between evaluation and sudden death was 4 ± 4 months. Rehospitalization until death or transplantation occurred in 11 patients at 1.7 ± 1.2 months after evaluation, all within the 1st 6 months. Of these 11, 6 were admitted with refractory fluid retention, 3 with unstable angina and 2 with persistent evidence of ischemia after an episode of sustained ventricular tachycardia. Transplantation was performed on an inpatient basis in 5 of the 11 patients and the other 6 died of progressive hemodynamic failure, which resulted from new infarction in 2 and was exacerbated by systemic infection in 2. Two patients died of heart failure at home.

By 6 months after evaluation and discharge, 94 patients remained in the follow-up study on tailored medical therapy. After the 1st 6 months, there were 11 sudden deaths; no patients died of hemodynamic decompensation or required readmission to await transplantation in hospital. By 12 months, 53 patients remained. There were four subsequent sudden deaths and no hemodynamic decompensation result-

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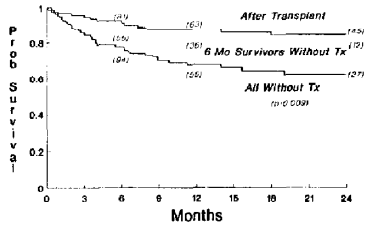

Figure 1. Actuarial survival curves calculated according to the Kaplan-Meier method from the time of evaluation for 214 patients discharged on medical therapy after transplant evaluation, a subset of 94 patients surviving the 1st 6 months after evaluation without transplantation (Tx) and 88 patients from the outpatient waiting list after transplantation. Numbers in parentheses refer to patients remaining at follow-up. Prob = probability of.

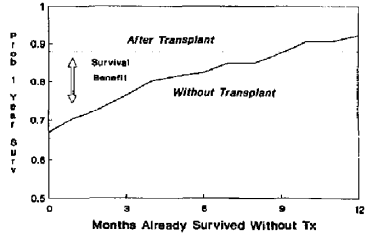

Figure 2. Improvement in probability (Prob) of 1-year survival (Surv) expected after transplantation (Tx) for patients waiting at home. The probability of 1-year survival without transplantation was obtained by recalculating the subsequent 1-year actuarial survival rate after each month of survival without transplantation for 214 patients discharged after evaluation (see Methods). The expected survival rate after transplantation was obtained in 88 patients who waited at home until transplantation.

ing in death or urgent transplantation in this group. The follow-up period on medical therapy without transplantation extended to 24 months for 27 patients.

Survivors versus nonsurvivors. There were no criteria that reliably distinguished individual survivors from nonsurvivors at the time of initial hospital discharge (Tables 1 and 2). Ejection fraction, history of previous vasodilator therapy and initial hemodynamic variables, including filling pressures, were not different between the two groups. On average, orthopnea and right-sided congestion were less severe, whereas serum sodium was slightly higher and filling pressures achieved after aggressive therapy were lower in survivors, who were also slightly older.

Survival of patients undergoing transplantation. Actuarial survival of the patients who underwent transplantation after waiting at home was 88% at 1 year (Fig. 1), comparable to that reported for other major programs (3,13). This survival rate is significantly better than the 67% for patients followed up on medical therapy ($p = 0.009$). Death after transplantation for outpatients was not related to the time spent waiting for a transplant and resulted from posttransplantation complications of rejection or infection >1 month after transplantation, except in one patient who died of right heart failure at 3 days.

Expected survival after waiting. The actuarial survival measured after transplantation does not reflect the deaths occurring in those on the waiting list. Because 75% of the deaths during 24 months after evaluation occurred within the 1st 6 months, the likelihood for survival without transplantation improved in outpatients who survived that initial 6 months. The expected survival for the next 12 months in patients who had already survived the 1st 6 months was 83% (Fig. 1). By 9 months after evaluation, the projected subsequent 1-year survival was 88%, whether or not transplantation was performed at that time.

The 1-year survival benefit was calculated as the difference between the predicted 1-year survival rate with transplantation and that without transplantation recalculated after each month already survived on medical therapy after evaluation (Fig. 2). The expected benefit decreased as patients waited longer until transplantation and was not evident at 9 months.

For purposes of comparison, the 1-year survival rate after transplantation was also calculated for the 64 patients of urgent status during the same period who underwent transplantation while waiting in the hospital during treatment with inotropic infusions or mechanical assist devices. Although the early operative mortality rate in these patients was 6% (4 of 64 patients) compared with only one early death in the 88 outpatients with transplantation, the 1-year actuarial survival rate of this group was 84%, which was not significantly different from the 88% in the outpatient group.

Discussion

Survival with advanced heart failure. This study of 214 outpatients with heart failure who were potential transplant candidates demonstrates that the major risks are from sudden death, hemodynamic decompensation or an ischemic syndrome during the 1st 6 months after referral. Patients who have survived that period of jeopardy without transplantation are at much lower risk during the next year; thus, the survival benefit to be expected from transplantation in outpatients after the 1st 6 months is small compared with that gained by critically ill inpatients or that which would be gained by outpatients who underwent transplantation immediately after evaluation.

The patients in this study are representative of those

selected for transplantation by current criteria in major centers (7). Patients with a low ejection fraction without a history of clinical decompensation were excluded, as were outpatients with nonischemic cardiomyopathy of recent onset. The severity of compromise of cardiac function in the selected patients is reflected by the clinical profile, including an average ejection fraction of 0.17, serum sodium of 135 mEq/liter (14) and class III or IV symptoms. In addition, the hemodynamic profile included an average initial cardiac index of 2 liters/min per m^2 and pulmonary capillary wedge pressure of 26 mm Hg, with those patients subsequently able to achieve the lowest filling pressures on therapy having a better prognosis, as previously described (15). Eligible patients refusing to accept transplantation were not excluded from analysis because they have been shown to have a high mortality rate without transplantation (16). The early mortality rate in our patients without transplantation is comparable with that of patients awaiting transplantation in five major centers, reported as 9% to 22% in 1986 (17) when average waiting periods were <3 months. Thus, although the data on subsequent outcome without transplantation may *retrospectively* identify some patients who may not have needed transplantation when listed, the decisions made at the time of evaluation were in accordance with current standard practice.

Survival on tailored medical therapy. As the reported 1-year survival rate after transplantation (13) has improved from 44% to 85%, the survival rate in patients with advanced heart failure on medical therapy has also improved. In 1978, patients accepted for transplantation who did not undergo the procedure had almost no chance of survival at 6 months (18). Even in a more recent study (19), patients evaluated and considered too well for transplantation had poor survival when subsequent medical care was not systematically designed and continued. The benefit of empiric vasodilator therapy for heart failure has been shown in patients with less severe heart failure in the cooperative Veterans Administration trial (20) and the CONSENSUS trial (21). In many patients who do not respond to empirically designed therapy, therapy with vasodilators and diuretic drugs tailored to hemodynamic goals has allowed hospital discharge and prolonged survival without transplantation (1,2,15). The relative benefit of transplantation compared with current medical therapy should be estimated in groups of patients such as those in this study, which excluded patients ineligible for transplantation because of noncardiac illness or repeated noncompliance, which would also compromise the apparent efficacy of medical therapy.

Expected benefits of transplantation. For eligible outpatients with advanced heart failure, survival after transplantation remains significantly better than that with medical therapy. However, the major risk for these patients is during the period early after evaluation, with 75% of deaths occurring during the 1st 6 months, resulting primarily from sudden death at home at an average of 4 months after evaluation. Despite concern that longer waiting times would result in more deterioration, decompensation leading to urgent priority transplantation was not seen after the 1st 6 months from evaluation. The relatively high mortality rate early after referral has been previously described (4) in patients with heart failure.

Survival curves with and without transplantation are customarily compared by starting with the time of transplantation for recipients; thus, the mortality of patients on the waiting list for transplantation is overlooked. This omission has resulted in overestimation of the actual benefit of transplantation for outpatients, as currently provided in this era of a severely limited donor heart supply and long waiting lists. The benefit for outpatients is not the expected increase in the 1-year survival rate from 67% to 88% that would result if all patients underwent transplantation at the time of acceptance. Instead, with an average waiting time approaching 6 months, the increase expected for the average patient waiting at home would only be from 83% to 88% and would be even less as the waiting lists continue to grow.

If the survival benefit is less than initially projected for the waiting list survivor, what are the benefits offered by transplantation for functional status and quality of life? It has previously been shown (2,5) that many patients whose condition can be stabilized on medical therapy after evaluation achieve an exercise capacity and self-assessed quality of life after 1 year that are, although less than those of healthy individuals, similar to those achieved by a comparable group of patients undergoing transplantation. Outpatients with more severe functional compromise that persists despite prolonged survival while on a waiting list are generally identified by refractory fluid retention unresponsive to a flexible diuretic regimen, objective exercise testing that reveals peak oxygen consumption <12 to 14 ml/kg per min (22) or, in some cases, by uncontrollable angina or symptomatic ventricular arrhythmias.

Outpatients versus hospitalized patients. This limited benefit for the average survivor on a waiting list contrasts sharply with that gained by patients who remain hospitalized in critical condition until urgent transplantation can be performed. By definition of urgent status, such patients have a life expectancy of hours or days without transplantation. Furthermore, the functional status and quality of life are obviously unacceptable for such patients, who are bed bound and dependent on intensive hospital support with intravenous infusions or temporary mechanical devices. Even though such patients may have a slightly higher postoperative mortality rate, their overall survival is currently comparable to that of outpatient candidates, both in this study and in others (23), if selection is carefully performed. Thus transplantation offers a much larger benefit in terms of both survival and function when performed in critically ill patients than in outpatients on the current waiting lists.

Limitations. This study is limited by the relatively small number of patients available for 2 years of follow-up without transplantation. This limitation is inherent in any study of

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potential transplant candidates, many of whom will eventually receive an appropriate donor heart and then be removed from the group of patients with heart failure on medical therapy. This study was not designed to identify specific risk factors for death in advanced heart failure, which have been previously addressed (15,22,24–26). In addition, it was not designed to demonstrate the efficacy of various medical regimens. Instead, it was performed to test the hypothesis that the expected survival benefit from transplantation decreases as waiting time increases for outpatient candidates receiving tailored medical therapy, as currently available, from the time of transplant evaluation.

Implications for candidate selection. The results of this study support the current policy of awarding higher priority to critically ill inpatients who are otherwise eligible than to waiting outpatients (27), in whom the expected benefits are lower. However, the majority of patients listed and a slightly smaller majority of patients undergoing transplantation are outpatients (3). Among these patients, the waiting list time is currently the major factor in priority, a policy not supported by this study.

Decisions regarding the selection and priority for outpatient transplantation would be facilitated if it were possible to identify those patients in greatest jeopardy for deterioration or death while on a waiting list. The patients with obvious hemodynamic instability that persists after adjustment of therapy during transplant evaluation are at greatest risk for hemodynamic deterioration, are easily identified (2) and are often rehospitalized before transplantation. However, for those patients whose condition can be stabilized, the major risk is of sudden death rather than late circulatory decompensation (2,15,22,28). Although multiple risk factors for sudden death have been identified, such as low ejection fraction due to coronary artery disease (15), persistent high ventricular filling pressures despite aggressive therapy (15), low exercise tolerance (22,25), low serum sodium (14), atrial fibrillation (29) and history of previous cardiac arrest (19,30), these variables are less useful criteria for an individual patient than for groups of patients. The use of programmed electrical stimulation or signal-averaged electrocardiography has not identified the majority of patients at risk (31,32). There are diverse causes of the sudden deaths that occur in patients with heart failure (33), for whom there is not adequate information at this time regarding the benefit of specific therapies aimed at prevention.

The ability to better select those outpatients at highest risk for sudden death, despite currently available drugs and devices, would allow us to award them a higher priority for transplantation. If their waiting times were short, the waiting list mortality rate would be reduced and the expected survival benefit would be realized. Until we can better select outpatients at risk, however, the information provided by the grim natural selection process of the waiting list should not be ignored. Those patients who survive for 6 months without transplantation deserve specific reevaluation, rather than receiving a higher priority. Persistent hemodynamic instability, angina or low maximal oxygen consumption may indicate the continued need for transplantation (2,22). However, in the absence of these factors, patients surviving for 6 months may not derive substantial benefit in functional capacity or survival from late transplantation.

The psychologic price paid by transplant candidates on a waiting list is high. There is a natural reluctance on the part of both physician and patient to remove from the transplant list a candidate whose life has been disrupted by the possibility of imminent transplantation. However, patients whose condition has been stable for 6 months often ask if transplantation is still necessary. For these survivors, the timing of transplantation is crucial not only to ensure that the procedure offers them sufficient immediate benefits, but also to maximize their total life expectancy (pretransplant plus posttransplant) because long-term survival after transplantation is limited by the graft atherosclerosis that affects almost 50% of recipients by 3 years (34).

There are currently twice as many heart transplant candidates joining the U.S. waiting list each month as there are patients actually undergoing transplantation (27). Criteria for selection and timing of transplantation must evolve to reflect the increasing impact of this resource limitation (35). To maximize the value of cardiac transplantation, we must learn how to best match the few available hearts with those recipients most likely to derive major benefit.

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