Survival and Quality of Life in Patients With Cardiac Resynchronization Therapy for Severe Heart Failure and in Heart Transplant Recipients Within a Contemporary Heart Failure Management Program

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Background: Current treatment of advanced chronic heart failure comprises pharmacologic approaches, multidisciplinary management strategies and device therapy. We sought to compare the outcome after cardiac synchronization therapy (CRT) with the outcome after heart transplantation within a contemporary heart failure management program.

Methods: In a cohort study, survival and quality of life were assessed in 105 patients who had received CRT (53% with defibrillator) for severe heart failure and in 112 heart transplant recipients attending a heart failure clinic at a tertiary hospital. For assessment of health-related quality of life the Medical Outcome Short Form 36 (SF-36) was applied to the survivors. A propensity score for receiving transplantation vs CRT was developed using logistic regression and was incorporated into statistical models.

Results: Severity of heart failure before heart transplantation or CRT was similar. Survival was not different between device recipients and transplant recipients by Kaplan–Meier analysis. Cox regression analysis with time-dependent covariates revealed a significant interaction between treatment and time, which favored transplantation late after intervention. There were no significant differences in 7 of 8 subjective measures of health-related quality of life. The score for physical functioning was higher in the transplantation group; this difference remained of borderline significance after multivariate adjustment.

Conclusions: Contemporary management of patients with advanced heart failure including CRT leads to improved survival and quality of life and diminishes the difference in these outcomes between conservative management and heart transplantation within the time-frame studied. Patient selection for heart transplantation requires consideration of these results. J Heart Lung Transplant 2008;27:746–52. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

In the current era, survival for heart failure patients has improved significantly.[1] This is a result of improved pharmacologic treatment,[2–5] multidisciplinary management strategies[6,7] and device therapy, such as cardiac resynchronization therapy (CRT) and defibrillator therapy.[8–12] Results of the German COCPIT study suggest that cardiac transplantation is associated with a survival benefit only in patients with a predicted high risk of dying on the waiting list.[13] Both heart transplantation and medical/device therapy have been shown to improve quality of life in advanced heart failure.[10,14] It was the aim of the present study to compare survival and quality of life in patients with severe heart failure under optimal multimodal therapy, including CRT, with heart transplant recipients managed within a comprehensive heart failure program.

METHODS

Patients

This cohort study included consecutive 217 patients from a heart failure and heart transplantation clinic: 105 heart failure patients were under optimal medical treatment and had received CRT with (53%) or without (47%) a defibrillator within the period 1997 to 2004; 112 patients had undergone heart transplantation within the period 1981 to 2004 and 48 patients within the period 1997 to 2004 (new era). Thirteen patients (3

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transplant and 10 CRT patients) with incomplete data sets were excluded. All CRT patients were included regardless of their hemodynamic response to CRT.

All patients were seen by a heart failure specialist at the heart failure and heart transplantation clinic at least four times per year. Visits included physical examination, adjustment of medication, patient education and counseling and multidisciplinary treatment of comorbidities. Close telephone contact with the patients was maintained by heart failure nurses and/or physicians. Baseline parameters collected at the time of intervention (device/transplantation) are shown in Table 1.

Device Therapy

Patients received a biventricular cardioverter-defibrillator (Attain System with InSync Marquis, Medtronic, $n = 34$; or Aescula System with Epic HF V-339, St Jude Medical, $n = 22$) or a biventricular device without a defibrillator (Attain System, Medtronic, $n = 21$; or Aescula System, St Jude Medical, $n = 28$). The pacing devices were tested and optimized twice per year. The best atrioventricular interval was set for maximal transmitral diastolic filling without premature termination of atrial filling as determined by Doppler echocardiography. The VV interval was set to zero for all patients.

Heart Transplantation

Orthotopic heart transplantation was performed without routine induction therapy. Routine immunosuppressive therapy consisted of cyclosporine, azathioprine or mycophenolate mofetil and prednisone.

Survival

Follow-up for patients no longer attending the heart failure clinic was performed using a questionnaire that was sent to the patients. When patients did not answer the questionnaire, they were contacted by telephone. The next step was to contact each patient's primary physician and then the local registration office.

Table 1. Patients Characteristics

	Medical/device	Heart transplants (all)	*p*	Heart transplants (new era)	*p* (vs device)
n	105	112		48	
Male	70%	87%	<0.05	92%	<0.05
Age (years)					
Median	66	56	<0.05	56	<0.05
Interquartile range	61–71	48–60		47–60	
Body mass index	25 ± 3	25 ± 4	NS	25 ± 3	NS
Ejection fraction (%)					
Median	20	20	NS	20	NS
Interquartile range	20–26	20–25		20–25	
Ischemic etiology	51%	47%	NS	52%	NS
NYHA Class III or IV	92%	98%	NS	100%	NS
CCS class I/II/III/IV (%)	5/15/19/0	1/10/35/7	<0.05	2/7/33/4	<0.05
Mean blood pressure (mm Hg)	91 ± 18	86 ± 12	<0.05	86 ± 18	NS
Heart rate (1/min)	82 ± 14	78 ± 16	NS	79 ± 15	NS
Atrial fibrillation	14%	30%	<0.05	31%	<0.05
QRS width (ms)	165 ± 30	129 ± 42	<0.05	140 ± 43	<0.05
Diabetes mellitus	21%	25%	NS	21%	NS
Hypertension	56%	52%	NS	42%	NS
History of smoking	49%	42%	NS	40%	NS
Family history for CAD	28%	31%	NS	35%	NS
Creatinine (mg/dl)					
Median	1.3	1.0	<0.05	1.1	<0.05
Interquartile range	1.1–1.5	1.0–1.2		1.0–1.3	
Serum sodium (mmol/ml)	139 ± 4	137 ± 4	<0.05	138 ± 4	NS
Cholesterol (mg/dl)					
Median	189	180	NS	186	NS
Interquartile range	169–220	180–190		168–192	
Defibrillator	53%	29%	<0.05	29%	<0.05
β-blocker	90%	52%	<0.05	79%	NS
ACEI or ARB	85%	69%	<0.05	86%	NS
Spironolactone	65%	36%	<0.05	47%	NS
Digitalis	66%	80%	NS	82%	NS
Statin	49%	21%	<0.05	25%	<0.05

NS, not significant; CAD, coronary artery disease.

Health-related Quality of Life

For assessment of health-related quality of life, the German version of the Short Form 36 (SF-36) questionnaire[15] was applied to 74 survivors in the device group and 49 survivors in the transplantation group (29 from the new era). One survivor in the device group and 4 survivors in the transplantation group did not complete the questionnaire.

The questionnaire is designed for self-administration and consists of a multi-item scale obtaining 8 health concepts perceptions.[16] SF-36 scores were normalized by dividing the scores for each patient and item by age- and gender-matched values from a German normative population sample. A health index was calculated for every patient as the mean of the normalized scores of the 8 items.

Statistical Analysis

Data are expressed as mean ± standard deviation unless indicated otherwise. Differences in continuous variables were assessed using Student's *t*-test for unpaired samples, and categoric variables were tested by chi-square test. Normal distribution of the data was assessed with a 1-sample Kolmogorov–Smirnov test to indicate the appropriateness of parametric testing. Differences for non-parametric data were assessed using the Mann–Whitney *U*-test. Cumulative survival was analyzed by the Kaplan–Meier method, and groups were compared with the log-rank test. A propensity score was developed using a logistic regression model to summarize predictors for receiving transplantation vs CRT. Variables (Table 1) and time to follow-up were entered into a logistic regression model using backward selection (inclusion at 0.05, exclusion at 0.1). Thus, a propensity score or a predicted probability for receiving transplantation vs CRT was obtained. The propensity score was then incorporated into statistical models for analysis of survival and quality of life to adjust for non-randomization.

Because the assumption of proportional hazards for treatment was violated, Cox regression analysis with time-dependent covariates was applied for survival analysis. The propensity score was entered in a first block. In a second block, variables (Table 1) with $p < 0.1$ in univariate analysis and variables with reported prognostic relevance in heart failure or after heart transplantation were entered into a multivariate Cox regression model with time-dependent $[f(t) = t]$ covariates using backward selection (inclusion at 0.05, exclusion at 0.1).

Internal consistency of the various items of the SF-36 was assessed using Cronbach's alpha coefficient. A Cronbach's alpha >0.7 is considered to denote acceptable agreement.[17]

The effect of treatment on SF-36 scores was assessed by linear regression analysis to adjust for covariates. In a first block, variables from Table 1 with $p < 0.1$ on univariate analysis, including time to follow-up and the propensity score, were entered into a multivariate linear regression model using backward selection (inclusion at 0.05, exclusion at 0.1). Treatment (transplantation or medical/device therapy) was entered in a second block. The effect of treatment was expressed as B coefficients with 95% confidence intervals. Statistical analyses were performed using SPSS, version 12.0.1 (SPSS, Inc., Chicago, IL). Levels of significance were not adjusted for multiple comparisons.

RESULTS

Patient Population

Seven CRT patients were on the waiting list for transplantation (none highly urgent) and 2 of them crossed over to transplantation during follow-up. The majority of the remaining CRT patients were either potential waiting list candidates with regular re-evaluations or considered ineligible mainly because of advanced age and comorbidities. Non-eligibility was based on the assessment of the interdisciplinary heart failure team. Ten heart transplant recipients (7 from the new era) were listed as highly urgent and 1 was on an intra-aortic balloon pump prior to transplantation. None was on a left ventricular assist device. Six heart transplant patients had a CRT device implanted prior to transplantation.

Severity of heart failure by New York Heart Association (NYHA) class before device implantation and transplantation was similar (Table 1). Medical/device patients were older, less likely to be male, had a higher mean blood pressure, less atrial fibrillation, a wider QRS interval and higher serum concentrations for creatinine and sodium. There were no significant differences between the two groups regarding heart rate, ejection fraction, body mass index, ischemic etiology, diabetes mellitus and hypertension. When only patients from the era 1997 to 2004 were analyzed, mean blood pressure and serum sodium concentration were not different between the groups.

Medical heart failure therapy was nearly optimal in medical/device patients (Table 1). Before transplantation, heart failure medication use was lower than in CRT patients. For patients from the new era, use of β-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), spironolactone and digitalis was not different between the groups.

Logistic regression revealed that significant predictors for transplantation vs CRT were younger age, male gender, lower cholesterol, QRS duration <120 ms and

time to follow-up. Medical heart failure therapy was not retained in the final model.

Survival

The median follow-up period was 791 days (interquartile range 331 to 1,340 days) for the medical/device group, 2,100 days (interquartile range 429 to 3,523 days) for all heart transplant recipients and 1,401 days (interquartile range 347 to 2,246 days) for heart transplant recipients from the new era. Thirty medical/device patients and 59 heart transplant recipients died during follow-up. Kaplan–Meier survival curves for the two groups are shown in Figure 1A. Survival was not different between heart failure patients and transplant recipients by Kaplan–Meier analysis (p = non-significant [NS]). Survival in device patients and transplant recipients was 84% vs 78% at 1 year, 80% vs 75% at 2 years and 70% vs 70% at 3 years. Survival was also not statistically different between groups when patients from the same era were compared (p = NS) (Figure 1B).

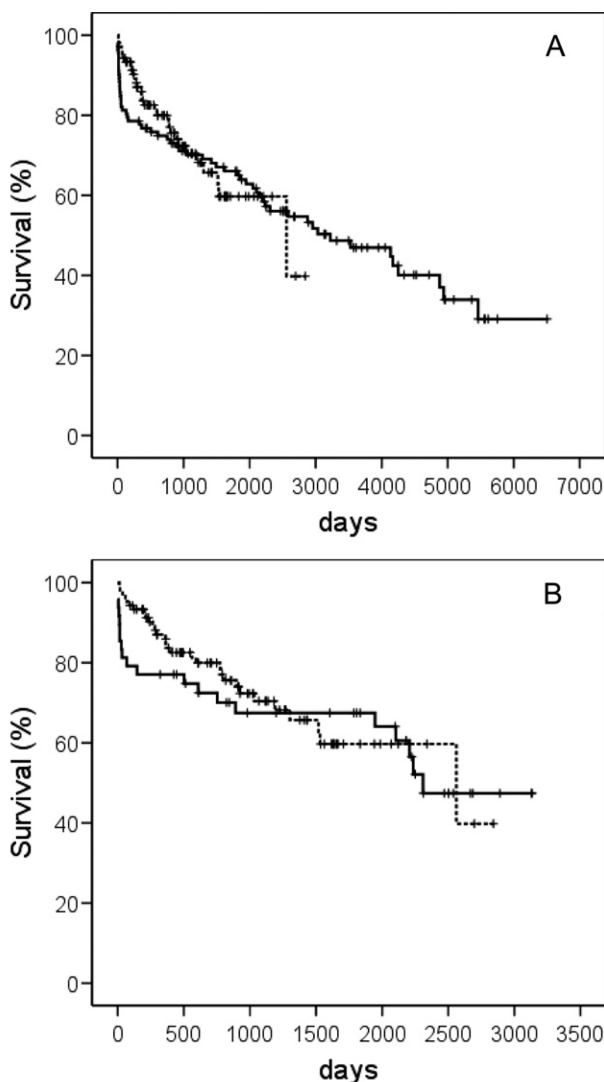

Figure 1. (A) Kaplan–Meier survival analysis for medical/device patients (broken line) and heart transplant recipients (solid line). (B) Kaplan–Meier survival analysis for medical/device patients (broken line) and heart transplant recipients (solid line) from the new era (1997 to 2004). For (A) and (B), p = NS by log-rank test.

Multivariate Cox regression analysis with time-dependent covariates revealed an interaction of treatment and time favoring transplantation late after intervention (Table 2). Treatment (transplant or CRT) was not retained in the final model. Similar results were obtained when the analysis was restricted to patients from the new era (Table 2, Model 2). Survival for the medical/device group, as predicted by the Seattle Heart Failure Model,[18] was 83% at 2 years. Predicted 2-year survival for actual non-survivors was significantly lower than for actual survivors (75% vs 85%, $p < 0.01$). Default values of the model were used for some of the variables that were not available in this data set.

Health-related Quality of Life

The internal consistency of the SF-36 was sufficient, with a Cronbach's alpha of 0.89. Measures of health-related quality of life showed no significant differences between the two groups for social functioning, physical and emotional role limitations, bodily pain, vitality, general health perceptions and mental health (Figure 2). Scores in each group for each item were significantly lower than the scores of a normative German male population sample.[19] The score for physical functioning was higher in the transplantation group (56 ± 32 vs 41 ± 30, $p < 0.05$).

B coefficients with 95% confidence intervals after multivariate regression are shown in Figure 3. Transplant recipients showed strong trends for better physical functioning ($p = 0.08$ for all patients and $p = 0.05$ for patients from the new era) and better general health perception ($p = 0.06$ for all patients and $p = 0.09$ for patients from the new era). An analysis in which SF-36 scores for each item and each patient were normalized for gender and age using a normative German population sample[19] ($n = 6,964$) yielded similar results. The health index was 0.70 ± 0.33 for heart failure patients and 0.74 ± 0.29 for heart transplant recipients (p = NS).

Predictors for the 8 SF-36 items after multivariate modeling (all patients) were: serum sodium, smoking status (physical functioning), smoking status, gender, time of intervention (physical role), Canadian Cardiovascular Society (CCS) class, smoking status, age, gender, presence of atrial fibrillation, propensity score (bodily pain), CCS class, hypertension, body mass index, NYHA class, serum sodium (general health perception), CCS class, hypertension, smoking status (vitality), CCS class, presence of atrial fibrillation, serum creatinine (social functioning), CCS class, smoking status,

Table 2. Multivariate Cox Regression Analysis

Parameter	Wald χ^2	Exp(B) (95% CI)	p
Model 1 (all patients)			
Creatinine	29.6	6.8 (3.4–13.6)	<0.05
Device therapy and time interaction	13.4	0.999 (0.998–0.999)	<0.05
Male gender	11.1	0.13 (0.04–0.43)	<0.05
Cholesterol	8.8	0.988 (0.980–0.996)	<0.05
Propensity score	6.1	3.8 (1.3–10.8)	<0.05
Digitalis use	5.5	0.4 (0.17–0.85)	<0.05
Body mass index	5.0	0.9 (0.81–0.99)	<0.05
Hypertension	3.7	1.8 (0.99–3.34)	NS
Age	3.6	1.0 (0.99–1.07)	NS
Model 2 (new era)			
Creatinine	34.8	11.3 (5.1–25.4)	<0.05
Male gender	13.7	0.07 (0.02–0.29)	<0.05
Cholesterol	13.5	0.984 (0.975–0.992)	<0.05
Body mass index	7.2	0.86 (0.77–0.96)	<0.05
Device therapy and time interaction	6.9	0.999 (0.998–1.000)	<0.05
Digitalis use	6.0	0.275 (0.10–0.77)	<0.05
Hypertension	5.2	2.28 (1.12–4.60)	<0.05
Time of intervention	3.5	0.81 (0.64–1.01)	NS
Propensity score	0.4	0.64 (0.17–2.45)	NS

ACEI or ARB medication, family history of coronary artery disease (emotional role), gender, CCS class, smoking status and serum creatinine (mental health).

DISCUSSION

Survival

The CARE-HF trial[10] and the COMPANION trial[11] reported 2-year survival rates of 82% and 74%, respectively, after CRT implantation. We observed a 2-year survival of 80% in patients with comparable heart failure severity who were not managed within a controlled trial. The registry of the International Society for Heart and Lung Transplantation (ISHLT)[20] reported 2-year survival after heart transplantation of 78% for the period 1993 to 1998 and 81% for the period 1999 to 2003. Survival rates in this study were consistent with these results.

In the landmark COCPIT study, transplantation did not improve 1-year survival risk for the total cohort of waiting list patients and only patients with the highest heart failure severity had a survival benefit.[13] Follow-up

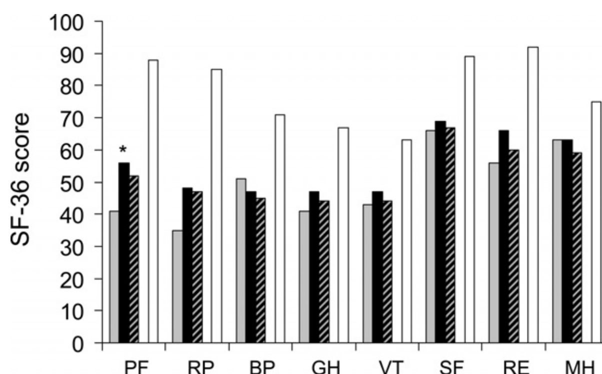

Figure 2. Health-related quality of life (SF-36) in medical/device patients (shaded bars), heart transplant recipients (filled bars) and heart transplant recipients form the new era (striped bars). The score for physical functioning was significantly higher in heart transplant recipients (*$p < 0.05$). Scores in each group for each item were significantly lower than the scores of a normative German male population sample (open bars). PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; ME, mental health.

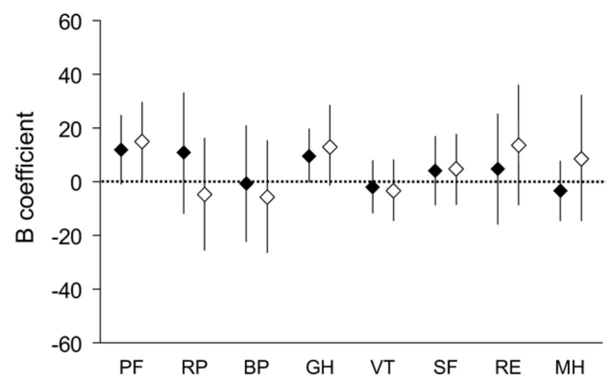

Figure 3. Effect of heart transplantation vs medical/device therapy on health-related quality of life (SF-36) after multivariate adjustment. B coefficients with 95% confidence intervals obtained from multivariate regression analysis are shown. Filled diamonds: all patients; open diamonds: patients from the new era (1997 to 2004). For physical functioning, p-values were 0.08 for all patients and 0.05 for patients from the new era. For general health, p-values were 0.06 for all patients and 0.09 for patients from the new era. PF, physical functioning; RP, role physical, BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; ME, mental health.

was limited to 1 year and heart failure therapy for waiting list patients was not specified. Data from 4,255 patients with stable advanced heart failure listed as United Network for Organ Sharing (UNOS) Status 2 showed no survival benefit from transplantation at 365 days.[21] Butler et al reported that survival in advanced heart failure had improved significantly with modern therapy.[22] The present study extends their findings in patients with greater use of modern heart failure therapies such as CRT, defibrillators, β-blockers and aldosterone antagonists. Our results are further supported by Vanderheyden et al, who showed that CRT effectively delays heart transplantation in end-stage heart failure.[23]

Quality of Life

Several quality-of-life (QOL) studies in heart transplant recipients have shown that patients' QOL improves significantly after surgery.[14] However, longer term follow-up data are scarce and there are few comparisons with advanced heart failure patients. Hummel et al[24] reported that heart transplant recipients had significantly better SF-36 scores than patients with advanced heart failure for the items "bodily pain," "general health perceptions" and "vitality." However, the group of heart failure patients was poorly characterized and it is not clear whether the population received the full benefit of modern heart failure therapy. From the studies by Hummel et al[24] and Politi et al,[25] it is clear that QOL assessed by SF-36 is significantly impaired in patients after heart transplantation as compared with the general population. Our study did not show any significant differences between patients with advanced heart failure and heart transplant recipients for 7 of the 8 SF-36 items after adjustment for covariates. However, transplant patients seemed to perform better in the physical functioning domain and possibly also in the general health domain. This is consistent with the general clinical impression and is supported by clinical data[9,26] that physical exercise capacity increases much more after transplantation than after device implantation.

Selection for Heart Transplantation

Regarding the shortage of donor organs, patients with a predicted low risk may be deferred from transplantation using pharmacologic approaches, device therapy (CRT and/or defibrillator) and multidisciplinary management strategies. However, a strategy to consider only the sickest patients for transplantation has its limitations. The ISHLT registry identified temporary circulatory support, mechanical ventilation and hospitalization at time of transplant—clinical settings not uncommon in high-urgency status—as significant predictors for 1-year mortality.[20] Allocation according to urgency and allocation according to maximal expected lifespan of the donated organ could be opposing imperatives. However, it seems to be clear that a predictive score or projected survival benefit estimation[27] must be applied to select patients appropriately for transplantation. Finally, given both the importance of the outcome of QOL and the paucity of data on this subject, more research is needed to estimate the expected QOL benefit after transplantation.

Study Limitations

Despite statistical adjustment with multivariate techniques the present study suffers from limitations generally inherent to observational studies. We attempted to adjust for non-randomization by inclusion of a propensity score into the statistical models. However, several sources of bias should be noted. Patients were possibly selected for transplantation because they were sicker than the average heart failure patient. On the other hand, transplant recipients patients may have represented a select group with less co-morbidity and therefore a better long-term outcome. Patient selection from different time periods may have biased our results. However, an analysis restricted to the patients from the new era, specifically 1997 to 2004, revealed similar results. Furthermore, the propensity analysis adjusted for the time of intervention. Nevertheless, one should be aware of possible differences in the populations not accounted for. Propensity methods can only account for variables that are measured.

The response rate to the QOL questionnaire was different between groups and data collection was incomplete. The response rate was mainly limited by the patients' deaths and was 99% in CRT survivors and 92% in transplant survivors.

There are more specific tools for assessment of QOL in heart failure patients, such as the Minnesota Living with Heart Failure Questionnaire. The results may have been different between the groups if more specific tools had been used. However, this was a comparison of two different populations and these tools were developed for heart failure. We therefore chose to use the more general SF-36 questionnaire.[25] In forthcoming larger multicenter studies, additional, more specific tools should be used.

Peak oxygen uptake values were not obtained for all patients. Thus, we could not include this parameter in our analysis. This important prognostic parameter would have permitted a better characterization of the severity of heart failure in the two populations.

Finally, our investigation was a single-center study with relatively small patient numbers. The statistical power to detect significant differences between groups was not sufficient to draw definite conclusions. A larger multicenter study is needed to compare current heart transplant patients with multimodality-treated heart fail-

ure patients and to validate our findings with regard to survival and QOL.

In conclusion, contemporary treatment of patients with severe heart failure, including CRT, within a comprehensive heart failure management program leads to improved survival and QOL and diminishes the difference in these outcomes between conservative management and heart transplantation within the time-frame studied. Heart failure risk scores and heart transplantation eligibility and selection criteria need to be re-evaluated continuously in the context of constantly improving therapies for severe heart failure that include advances in medical, device and management strategies.

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