# Prognosis of Heart Transplant Candidates Stabilized on Medical Therapy

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**Introduction and objectives.** A significant percentage of patients selected as candidates for heart transplantation can be stabilized by medical treatment, thereby enabling indefinite postponement of inclusion on the operation list. The aim of this study was to investigate the prognosis of these patients.

**Patients and method.** We studied retrospectively 118 patients with severe left ventricular systolic dysfunction (ejection fraction ≤35%) who were consecutively evaluated for cardiac transplantation but who did not undergo transplantation because they became clinically stable on medical treatment. The mean follow-up period was 2.14 (2.19) years. Kaplan-Meier survival analysis, and univariate and multivariate Cox proportional risk analyses of factors predicting survival were performed.

**Results.** There were 18 deaths (15.2%): 12 were sudden (66.7%), 5 were due to heart failure (27.8%), and 1, to a non-cardiac cause (5.5%). The survival rate was 88% in the first year and 82% in the following 2 years. Univariate analysis showed that the parameters associated with mortality ($P \leq .05$) were pulmonary artery and capillary wedge pressures, diuretic treatment, and the absence of beta-blocker therapy. In the multivariate analysis, only the absence of beta-blocker therapy remained statistically significant ($P = .003$; RR = 0.13; 95%CI, 0.03-0.50).

**Conclusions.** In a population of patients with severe left ventricular systolic dysfunction who were candidates for heart transplantation but who were stabilized by medical therapy, mortality during the first year of follow-up was 12%. Beta-blocker therapy was the only variable associated with better survival.

**Key words:** *Heart failure. Transplantation. Beta-blockers. Prognosis.*

**Pronóstico de una población inicialmente candidata a trasplante cardíaco controlada con tratamiento médico**

**Introducción y objetivos.** Un porcentaje importante de los pacientes evaluados como posibles candidatos a trasplante cardíaco logra, con tratamiento médico, una estabilización que permite posponer indefinidamente su entrada en lista. El objetivo de este estudio es determinar el pronóstico de estos pacientes.

**Pacientes y método.** Estudio retrospectivo de 118 pacientes con disfunción sistólica severa de ventrículo izquierdo (fracción de eyección ≤ 35%), consecutivamente enviados para valoración de trasplante cardíaco, no trasplantados por estabilización clínica con tratamiento médico. El seguimiento medio fue de 2,14 ± 2,19 años. Se elaboraron las curvas de supervivencia de Kaplan-Meier, se realizó un análisis univariable y se ajustó un modelo de riesgos proporcionales de Cox para analizar los factores predictivos de supervivencia.

**Resultados.** Murieron 18 pacientes (15,2%), 12 (66,7%) por muerte súbita, 5 (27,8%) por insuficiencia cardíaca y 1 (5,5%) por causa no cardíaca. La probabilidad de supervivencia el primer año fue de 0,88, y la de los 2 siguientes de 0,82. En el análisis univariable, las variables asociadas con la mortalidad ($p \leq 0,05$) fueron el valor de las presiones arterial pulmonar y capilar pulmonar, el tratamiento diurético y la ausencia de tratamiento con bloqueadores beta; esta última fue la única variable que mantuvo la significación en el análisis multivariable ($p = 0,003$; riesgo relativo, 0,13; intervalo de confianza del 95%, 0,03-0,50).

**Conclusiones.** En una población de pacientes con disfunción sistólica severa del ventrículo izquierdo, candidatos a trasplante cardíaco pero estabilizados con tratamiento médico, la mortalidad el primer año de seguimiento fue del 12%. El tratamiento con bloqueadores beta fue la única variable asociada con una mayor supervivencia.

**Palabras clave:** *Insuficiencia cardíaca. Trasplante. Bloqueadores beta. Pronóstico.*

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ABBREVIATIONS

ICD: implantable cardioverter-defibrillator.
ACE: angiotensin-converting enzyme.

## INTRODUCTION

The management of heart failure has improved in recent years by the introduction of new drug treatment regimens that have shown to improve patients' clinical status and to increase survival.[1-10] The majority of patients referred for assessment in heart transplant centers share a common characteristic of heart failure due to severe left ventricular dysfunction. Adequate treatment leads to an improvement in the functional class of a large number of such patients and allows their placement on the waiting list to be postponed despite the fact that they remain at increased risk, especially of sudden death.[11,12] In patients with left ventricular dysfunction who have a better functional class (New York Heart Association classes I and II), sudden death is responsible for more than 50% of fatalities[13,14] and the most common initial mechanism is ventricular tachyarrhythmia.[15] Use of an implantable cardioverter-defibrillator (ICD) has shown to reduce the occurrence of sudden death and improve the survival of groups of patients with severe ventricular dysfunction.[16-20]

The aim of this study was to describe a population of patients referred for heart transplant assessment who did not ultimately receive a transplant due to stabilization of their symptoms. Specific emphasis was placed on establishing prognosis and the factors that may be associated with it, along with the cause of death when it occurred.

## PATIENTS AND METHODS

### Selection of Patients

A retrospective study was undertaken in a group of patients with severe left ventricular systolic dysfunction (ejection fraction ≤35%) who were referred consecutively for assessment in the heart transplant unit of our hospital between January 1992 and July 2003 but who were not placed on the waiting list for transplant due to their good clinical condition following optimization of medical treatment. Initial assessment was aimed at establishing the indication for heart transplant, based on available guidelines,[21-23] and ruling out the availability of an alternative definitive treatment, as well as assessing contraindications for inclusion on the waiting list for transplant. Likewise, where possible, adjustments were made in medical treatment that could be optimized in subsequent appointments if indicated. Once the patient was stabilized, treatment-related data was collected along with data from laboratory analyses and ergometry with or without measurement of gas exchange; in all cases, the recorded data corresponded to that which was obtained closest to the last follow-up date.

Patients who presented an established contraindication for heart transplant at the initial assessment did not undergo follow-up and were, therefore, excluded from the study. Likewise, those patients who died during the initial assessment or whilst on the active transplant waiting list were excluded from the study.

During the study period, 444 patients were referred for assessment and, of those patients, 240 received a transplant. Of the remaining 204 patients, 86 (42.2%) were excluded: 16 (7.8%) due to absence of confirmed left ventricular systolic dysfunction, 61 (29.9%) as a result of contraindications for transplant identified during the initial assessment, and 9 (4.4%) as a result of death during the assessment or whilst on the waiting list for transplant. The remaining 118 patients underwent periodic follow-up on the basis of their good clinical condition; those patients constitute the study group.

Follow-up was considered to be complete when the patient was discharged due to sustained improvement of ventricular function (left ventricular ejection fraction >35%) or functional class, when the patient underwent an alternative definitive therapeutic procedure, or if, following a period of follow-up, a formal contraindication for transplant was established. Figure 1 shows the algorithm for inclusion and follow-up of the patients.

When death occurred the cause was investigated, considering sudden death as immediate and unexpected death, occurring in or outside of the hospital, in the absence of symptoms in the previous 24 hours indicative of myocardial ischemia or heart failure, including death occurring during sleep.[14,24] To this end, the patient chart was assessed. When the cause of death was not recorded in the patient chart, the patient's family or the doctors who had last attended the patient were contacted by telephone to obtain further information.

### Statistical Analysis

Categoric and continuous variables are shown as percentages or means±SD. Comparisons of subjects with and without events during follow-up were made using the $\chi^2$ test or the Fisher exact test for percentages and the Student *t* test for means of qualitative variables. Survival tables and curves were prepared according to the Kaplan-Meier method. The Mantel-Haenszel test (log-rank test) was used to compare the survival curves. The possible relationship between the

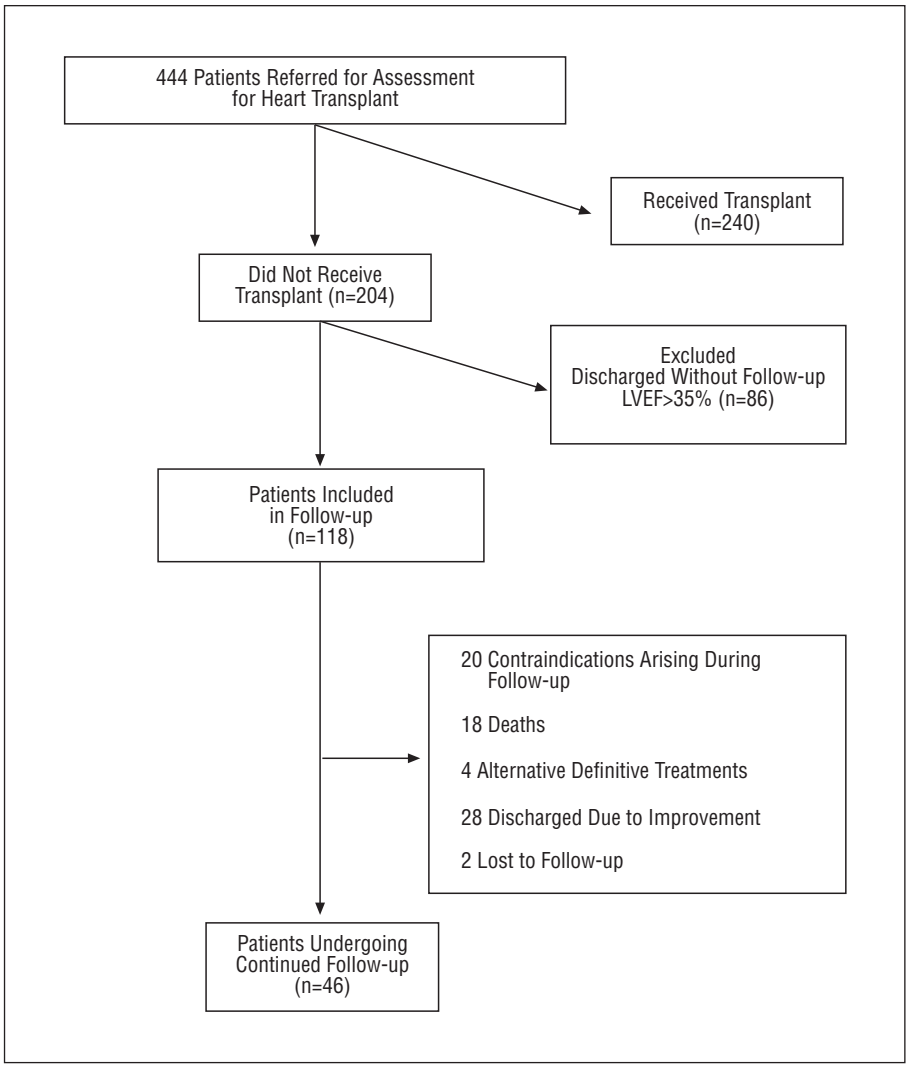


**Figure 1.** Algorithm for inclusion and follow-up of patients in the study. LVEF indicates left ventricular ejection fraction.

different variables and the occurrence of death was assessed by univariate analysis; statistical significance was established at $P<.05$ and a Cox proportional hazards model was fitted to analyze the effect of predictors of survival, including those variables with a value of $P<.10$ in the univariate analysis.

## RESULTS

Table 1 shows the clinical characteristics of the selected patients and the medical treatment used.

Right-heart catheterization was performed in 103 patients (87.3%) and ergometry was performed in 86 (73%). Since the hemodynamic and analytic data and the results of the effort test correspond to a time at which the treatment had been optimized, the parameters are all practically normal. Table 2 shows the clinical condition of the 118 patients at the final follow-up appointment. Figure 2 shows the survival curve for the 118 patients included in the follow-up. Eighteen patients (15.25%) died after a mean follow-up period of 1.19±1.2 years, with a median of 0.76 years (interquartile range, 0.32-1.75 years). The probability of survival in the first year was 0.88 and in the second and third years, 0.82. During the follow-up period, 4 patients received an alternative treatment that was considered definitive: 2 cases of aortic valve replacement in patients with severe aortic regurgitation initially referred for assessment for transplant due to very severe systolic dysfunction and in whom valve replacement was performed upon improvement of left ventricular systolic function; 1 case of surgical coronary revascularization; and 1 case of ablation of an ectopic ventricular focus with subsequent normalization of ventricular function. Only 1 of the 28 patients who were discharged on the basis of improved ventricular function or maintained stability of functional class had died after a mean follow-up period of 2.8±2.3 years following discharge.

An ICD was implanted in 23 of the 118 patients (19.5%); in 9 of those patients (39.1%) the device was implanted for secondary prevention, either due to prior

TABLE 1. **Clinical Characteristics of the Patients (n=118)***

| | |
|---|---|
| Age, years | 52.2±9.8 |
| Men, n (%) | 108 (91.5) |
| Underlying heart disease | |
| Ischemic, n (%) | 64 (54.2) |
| Dilated cardiomyopathy, n (%) | 46 (39) |
| Valvular, n (%) | 8 (6.8) |
| Evolution of heart failure, years | 3.39 (5.1) |
| NYHA functional class | 1.66 (0.79) |
| Serum creatinine, mg/dL | 1.16 (0.31) |
| Serum sodium, mmol/L | 139.8 (2.99) |
| Serum potassium, mmol/L | 4.3 (0.4) |
| Hemoglobin, g/dL | 14.2 (1.8) |
| LVEF | 23.6 (6.6) |
| Heart rate, beats/min | 81.6 (15.2) |
| MET in ergometry | 7.8 (2.8) |
| Peak $O^2$ consumption, mg/kg/min | 18.3 (6.1) |
| Presence of atrial fibrillation, n (%) | 29 (24.6) |
| Systolic arterial pressure, mm Hg | 113.4 (21.3) |
| Diastolic arterial pressure, mm Hg | 69.4 (11.9) |
| Cardiac output, L/min | 4.9 (1.25) |
| Cardiac index, L/min/$m^2$ | 2.6 (0.65) |
| Mean right atrial pressure, mm Hg | 5.9 (3.4) |
| Pulmonary capillary wedge pressure, mm Hg | 14.1 (0.8) |
| Pulmonary arterial pressure, mm Hg | |
| Systolic/diastolic | 35.2 (13.3)/15.5 (7.8) |
| Mean | 22 |
| Treatment | |
| ACE inhibitors, n (%) | 102 (86.4) |
| Angiotensin II receptor antagonists, n (%) | 14 (11.9) |
| Beta-blockers, n (%) | 68 (57.6) |
| Spironolactone, n (%) | 44 (37.3) |
| Digoxin, n (%) | 69 (58.5) |
| Diuretics, n (%) | 49 (41.5) |
| Hydralazine, n (%) | 23 (19.5) |
| Nitrates, n (%) | 54 (45.8) |
| Amlodipine, n (%) | 11 (9.3) |
| Amiodarone, n (%) | 6 (5.1) |
| Other antiarrhythmics, n (%) | 2 (1.7) |

*Data are shown as the mean±SD or number (%) if so specified. NYHA indicates New York Heart Association; LVEF, left ventricular ejection fraction; MET, metabolic equivalents; ACE, angiotensin-converting enzyme.

TABLE 2. **Situation of the Patients at the Final Follow-up**

| | |
|---|---|
| Death during follow-up | 18 (15.2%) |
| Sudden death | 12 (66.66%) |
| Heart failure | 5 (27.8%) |
| Noncardiac death | 1 (5.55%) |
| Discharge due to development of a contraindication | 20 (16.9%) |
| Discharge due to improvement | 28 (23.7%) |
| Ejection fraction >35% | 17 (60.7%) |
| Functional class | 5 (17.8%) |
| Functional class and relative contraindication | 6 (21.4%) |
| Alternative definitive surgery | 4 (3.4%) |
| Continuing programmed follow-up | 46 (39%) |
| Lost to follow-up | 2 (1.7%) |

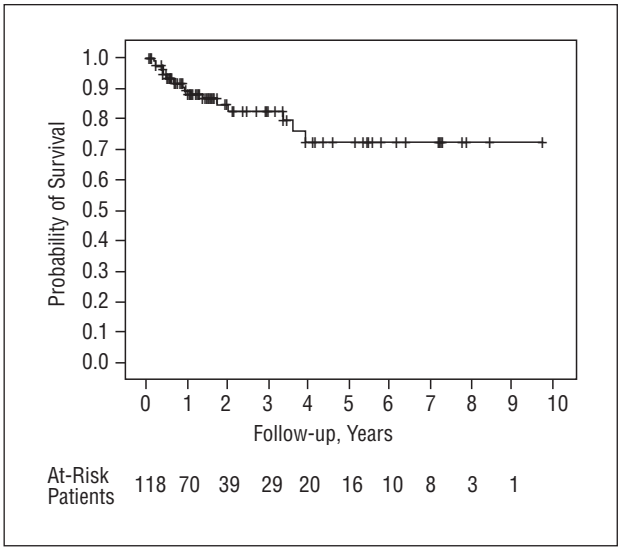


**Figure 2.** Survival curve for the 118 patients included in the follow-up (Kaplan-Meier).

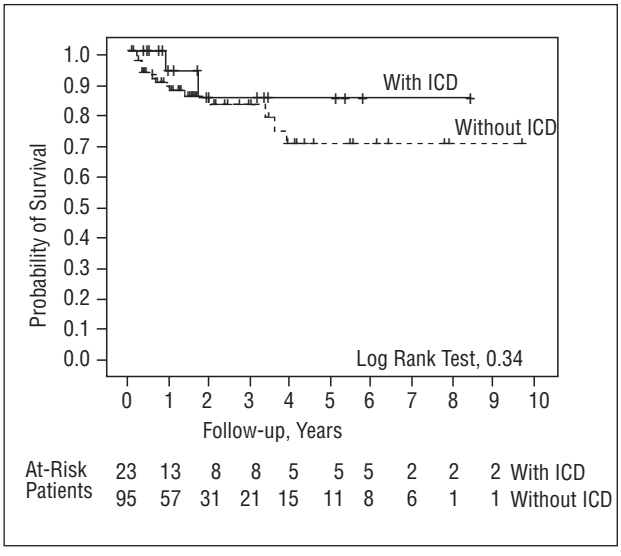


**Figure 3.** Survival curve (Kaplan-Meier) for the patients with (continuous line) or without (dashed line) an implantable cardioverter-defibrillator (ICD).

history of ventricular fibrillation (4 patients, 17.3%) or due to sustained ventricular tachycardia (5 patients, 21.8%). In 14 patients (60.9%), the indication for ICD implantation was primary prevention: in 12 cases (52.2%) for nonsustained ventricular tachycardia in patients diagnosed with ischemic heart disease and in 2 (8.7%) for syncope of unknown cause. Of the 23 patients who received an ICD, 2 (8.69%) died, both due to heart failure. Five patients (21.7%) with an ICD received treatment of arrhythmias, 3 with appropriate discharges and 2 by programmed stimulation to terminate a tachycardia. Figure 3 shows the survival curve for patients according to whether or not they had received an ICD. The probability of survival in the first

TABLE 3. **Univariate Analysis. Most Significant Predictors of Survival***

| Variable | *P* | RR (95% CI) |
|---|---|---|
| PCWP† | .008 | 1.08 (1.02-1.15) |
| MPAP† | .012 | 1.01 (1.01-1.10) |
| LVEF at last follow-up | .12 | 0.96 (0.91-1.01) |
| Spironolactone | .15 | 0.44 (0.14-1.33) |
| Use of other diuretics† | .009 | 3.68 (1.38-9.86) |
| Beta-blockers† | <.001 | 0.10 (0.03-0.35) |
| ICD | .35 | 0.50 (0.11-2.16) |

*RR indicates relative risk; CI, confidence interval; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary arterial pressure; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator.
†Statistically significant variables.

TABLE 4. **Multivariate Analysis***

| Variable | *P* | RR (95% CI) |
|---|---|---|
| PCWP | .280 | 1.08 (0.94-1.25) |
| MPAP | .432 | 0.95 (0.84-1.08) |
| LVEF at last follow-up | .307 | 0.97 (0.92-1.03) |
| Beta-blockers† | .003 | 0.13 (0.03-0.50) |
| Spirolactone | .813 | 0.86 (0.26-2.89) |
| Other diuretics | .326 | 1.88 (0.53-6.62) |
| ICD | .409 | 0.52 (0.11-2.43) |

*RR indicates relative risk; CI, confidence interval; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary arterial pressure; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator.
†Statistically significant variable.

year for patients with an ICD was 0.93 and in the second year, 0.85. No significant difference in the probability of survival was seen between patients who had received an ICD and those who had not.

Table 3 contains a summary of the variables that displayed the most statistically significant association with the occurrence of death in the univariate analysis. Table 4 shows the results of the multivariate analysis. Only treatment with beta-blockers maintained statistical significance (*P*=.003; relative risk [RR] =0.13; 95% confidence interval [CI], 0.03-0.50). Figure 4 shows the survival curves for patients according to treatment with or without beta-blockers. The reduced mortality in patients treated with beta blockers maintained its statistical significance in the reduction of sudden death (2 cases in patients treated with beta-blockers compared with 10 in those who did not receive beta blockers; *P*=.002; RR=0.27; 95% CI, 0.07-0.96) but not in the case of death caused by heart failure, probably due to the low number of events (1 death due to heart failure in the group treated with beta-blockers compared with 4 deaths in patients who did not receive beta-blockers; *P*=.16; RR=0.34; 95% CI, 0.06-1.96). Table 5 shows the clinical characteristics and treatment for both groups. Fewer of the patients treated with beta-blockers received digoxin and

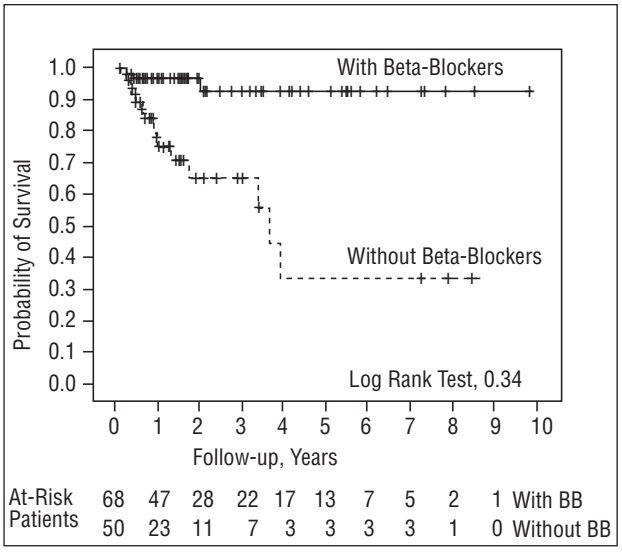


**Figure 4.** Survival curve (Kaplan-Meier) for the patients treated with (continuous line) or without (dashed line) beta-blockers (BB).

diuretics, whereas more of those patients received spironolactone; also, the group of patients selected after 1997 included a greater proportion of individuals treated with beta-blockers. The lower heart rate in patients treated with beta-blockers can be explained by the treatment itself, in the same way that the higher levels of serum potassium in that group is attributable to the higher percentage of patients treated with spironolactone.

## DISCUSSION

The target population of this study was made up of a group of patients who were in a sufficiently severe condition to have required assessment for heart transplant but in whom alternative treatment stabilized their clinical condition sufficiently to postpone inclusion on the transplant waiting list, at least for the duration of the follow-up that was undertaken. However, persistence of severe left ventricular systolic dysfunction means that those patients remain in a risk group. This is supported by the increased mortality displayed in this study—greater than 15% after more than 2 years of follow-up, with sudden death (67%) as the main cause of fatality. In our study, treatment with beta-blockers was the only significant predictor of survival.

### Previous Studies

Rickenbacher et al[24] studied a similar population of 116 patients with a mean follow-up period of 25±14.8 months; however, they did not exclude those patients who finally received a transplant from the analysis. The mean age of the population was 6 years less than

TABLE 5. **Comparison of Clinical Variables in the 118 Patients Grouped According to Treatment With or Without Beta-Blockers***

| Variable | Without Beta-Blockers (n=50) | With Beta-Blockers (n=68) | *P* |
|---|---|---|---|
| Sex, men | 90% | 92.6% | .610 |
| ICD implantation | 12% | 25% | .078 |
| Atrial fibrillation | 30% | 20.6% | .241 |
| Treatment, % | | | |
| ACE inhibitors | 88 | 85.3 | .671 |
| Spironolactone | 22 | 48.5 | .003† |
| Digoxin | 74 | 46.4 | .003† |
| Diuretics | 62 | 26.5 | <.001† |
| Angiotensin II receptor antagonists | 8 | 14.7 | .266 |
| Nitrates | 54 | 39.7 | .124 |
| Hydralazine | 30 | 11.8 | .13 |
| Antiarrhythmics | 2 | 1.5 | .097 |
| Age, years | 52.5±9.4 | 52.0±10.1 | .78 |
| Initial LVEF | 23.3±7.0 | 23.8±6.3 | .708 |
| Heart rate, beats/min | 85.5±15.5 | 78.8±14.5 | .021† |
| SAP, mm Hg | 112.9±23.0 | 113.7±20.0 | .855 |
| DAP, mm Hg | 68.6±12.1 | 69.9±11.7 | .549 |
| PCWP, mm Hg | 14.6±8.1 | 13.7±7.4 | .572 |
| SPAP, mm Hg | 36.5±14.8 | 34.4±12.0 | .461 |
| DPAP, mm Hg | 15.4±8.5 | 15.6±7.3 | .912 |
| MPAP, mm Hg | 23.3±10.6 | 22.0±8.5 | .521 |
| Right atrial pressure | 5.39±4.3 | 6.21±2.52 | .241 |
| Cardiac output, L/min | 4.98±1.31 | 4.85±1.21 | .626 |
| Cardiac index, L/min/m$^2$ | 2.69±0.76 | 2.56±0.55) | .319 |
| Hemoglobin, g/dL | 14.1±2.02) | 14.3±1.67 | .56 |
| Serum creatinine, mg/dL | 1.22±0.38 | 1.11±0.24 | .069 |
| Serum sodium, mmol/L | 139.3±2.57 | 138.5±3.23 | .147 |
| Serum potassium, mmol/L | 4.23±0.45 | 4.4±0.37 | .035† |
| Peak $O_2$ consumption, mg/kg/min | 17.33±4.18 | 19.29±7.56 | .29 |
| Years since diagnosis | 3.29±4.45 | 3.47±5.57 | .852 |
| Included prior to 1997 | 70.3% | 29.7% | <.001† |

*Qualitative variables are expressed as percentages and quantitative variables as means±SD.
ICD indicates implantable cardioverter defibrillator; ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; PCWP, pulmonary capillary wedge pressure; SPAP, systolic pulmonary arterial pressure; DPAP, diastolic pulmonary arterial pressure; MPAP, mean pulmonary arterial pressure.
†Statistically significant differences.

that of our study population and the proportion of patients suffering from idiopathic dilated cardiomyopathy was substantially higher than that of ischemic heart disease (69% vs 26%). Treatment did not include beta-blockers. Mortality during follow-up was 8%, a finding that was used to explain the fact that predictors of mortality were not identified in that study. Of the 9 deaths recorded, 7 were sudden (78%). In a similar population described by Nägele et al,[25] mortality following a mean follow-up period of 2.3±2.4 years was 26%, the majority of fatalities due to sudden death (72%). Age, percentage of men, and proportion of patients with ischemic heart disease were similar to our patient group. The percentage of patients treated with beta-blockers varied from 0% in the 95 patients selected during the first 5 years of the study (1984-1989) to 63% in those patients selected during the last year. Anguita et al[26] studied a population of 240 patients with severe heart failure who were assessed for possible heart transplant; the population contained a higher proportion of patients presenting dilated cardiomyopathy (65%) than ischemic heart disease. The overall follow-up period was 16±13 months. In a subgroup of 71 patients without initial indication for transplant due to their good clinical condition, 9 patients (13%) died, of whom 7 (78%) died suddenly.

Butler et al[27] performed a retrospective study of a population of 507 patients assessed in a single hospital for possible placement on the waiting list for heart transplant: 320 were assessed between 1993 and 1997 and 187 between 1999 and 2000. In the latter group, a greater proportion of patients were treated with beta-blockers (72% vs 10%) and spironolactone (41% vs 2%), and the use of a defibrillator was more common (19% vs 11%). The mean follow-up for both populations was 1 year, time during which efforts were made

to establish the prognosis, the main parameters being occurrence of death and requirement for ventricular assistance or urgent transplant. Such events were observed during the first year in 22% and 12% of the populations corresponding to the past and current eras, respectively, whereas in the second year the corresponding rates rose to 33% and 21%, respectively. An event-free survival of 81% was observed in patients with peak oxygen consumption between 10 and 14 mL/kg/min in stress tests with measurement of gas exchange. This increased to 86% if they were treated with beta-blockers and had an ICD. When the results were compared with survival in a population of 184 patients who received a transplant, with 88% and 84% survival in the first and second year, respectively, the authors concluded that the criteria for inclusion on the heart transplant waiting list should be revised, given the current improvement in survival of patients with heart failure.

Current treatment for heart failure is aimed not only at normalizing hemodynamic changes, such as increased filling pressure and cardiac output, but also at neutralizing the effects of compensatory neurohumoral activation, which, although offering short-term hemodynamic support, favor long-term progression of heart failure and shorten survival.[28,29] All of the patients included in our study received at least 1 vasodilator. They received an angiotensin-converting enzyme (ACE) inhibitor or, alternatively, an angiotensin II receptor antagonist (98% of patients). Beta-blockers were prescribed in an additional 58% of patients. Various clinical trials have demonstrated a beneficial effect of the beta-blockers carvedilol,[4,5] bisoprolol,[6] and metoprolol[7] in increasing survival of patients with left ventricular systolic dysfunction who were treated previously with ACE inhibitors, leading to around a 30% reduction in mortality; this reduction affects both the incidence of sudden death and that of death occurring due to worsening of heart failure. Following an initial period of myocardial depression linked to the suppression of adrenergic support, beta-blockers improve intrinsic myocardial systolic function and ventricular remodeling.[30]

## Influence of Implantable Cardioverter-Defibrillators on Prognosis

Implantation of an ICD is an established indication in patents with left ventricular dysfunction who have survived a prior episode of ventricular fibrillation or sustained ventricular tachycardia.[18,31] Previous studies have evaluated the effect of implanting an ICD in patients with heart failure. Böcker et al[17] undertook a retrospective study in a population of 603 patients in whom an ICD had been implanted for the treatment of sustained malignant ventricular tachyarrhythmia, aborted sudden death, or syncope attributable to ventricular tachycardia in the context of heart failure. The study population had a mean age of 57 years, 59% of patients had ischemic heart disease, and the patients had a mean ejection fraction of 44%. Based on an analysis of appropriate ICD discharges, those authors suggest that ICD implantation leads to an increase in survival that is more apparent initially in patients in New York Heart Association functional classes II and III (devices were not implanted in class IV patients), with an estimated 15% benefit in the first year and 23% benefit at 3 years. However, only 26% of the patients received beta-blockers and 57% ACE inhibitors. Similarly, Sweeney et al[16] performed a retrospective evaluation of the impact of ICD implantation on survival in 291 patients who were consecutively referred to be assessed for heart transplant, 59 of whom had received an ICD for aborted sudden death, sustained or nonsustained ventricular tachycardia, or syncope attributable to ventricular tachyarrhythmias, with a similar percentage of patients with ischemic heart disease compared with other etiologies, a mean ejection fraction of 19%, 85% of patients treated with ACE inhibitors, and only 10% of patients treated with beta-blockers, which were used more often in patients who had received an ICD. Fifty-six percent of the patients were placed on the transplant list. Despite the fact that patients with an ICD had a lower risk of sudden death, there was no difference in the overall risk of death after a follow-up period of 15 months. In the DEFINITE trial,[31] 458 patients with nonischemic dilated cardiomyopathy and a mean ejection fraction of 21% were randomized to receive standard medical treatment for heart failure or standard medical treatment along with implantation of an ICD. Most patients received ACE inhibitors and beta-blockers (86% and 85%, respectively). A reduced incidence of sudden death was observed in patients who received an ICD, but there was no reduction in the risk of death from any cause. Mortality as a result of sudden death (3.7%) was lower than expected. The authors justify this observation on the basis of the high proportion of patients treated with ACE inhibitors and beta blockers. Other authors have established the benefit of implanting an ICD in patients on the heart transplant waiting list.[19,32]

Although our patients were potential candidates for heart transplant, they were not placed on the waiting list due to their good functional class. Implantation of an ICD was not found to be a predictor of survival. This can probably be attributed to the low number of patients who received this treatment and the limited follow-up period. In fact, sudden death was the main cause of fatality in these patients. In addition, it should be taken into account that in our study the follow-up did not include patients who subsequently received a transplant, a group who appear to receive particular benefit from this treatment.[17,19,33]

The results of our study highlight the importance of using beta-blockers as part of the treatment in patients with severe ventricular systolic dysfunction whose good functional class allows indefinite postponement of their inclusion on the waiting list for heart transplant.

### Limitations of the Study

This study was retrospective, although few losses occurred during the follow-up period. The retrospective nature of the study places particular limitations on the classification of the cause of death. Furthermore, the long selection period led to the differences found in the treatment of the patients, the majority treated with beta-blockers after 1996 and with spironolactone after 1999, as a result of the reports of Packer et al[4] and Pitt et al,[8] respectively. This accounts for the much greater proportion of patients treated with beta-blockers who also received treatment with spironolactone, although the latter is not associated with improved survival. Nevertheless, given the retrospective nature of the study, we cannot exclude the possibility of a bias in the treatment of the patients such that those patients who received beta-blockers were in a better clinical condition. The sample size is modest, restricting the statistical power of the study.

## CONCLUSIONS

In a population of patients with severe left ventricular systolic dysfunction who were potential candidates for heart transplant but who were stabilized with medical treatment, mortality continued to be increased (12% in the first year of follow-up) and sudden death was the principal cause. Treatment with beta-blockers leads to notable improvement in the prognosis of this population.

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