THE IMPACT OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS ON MORTALITY AMONG PATIENTS ON THE WAITING LIST FOR HEART TRANSPLANTATION

Implantable cardioverter-defibrillators were investigated for their impact on mortality in 228 consecutive heart transplant candidates on the waiting list for transplantation (207 patients without and 21 with implantable cardioverter-defibrillator therapy). The mortality rate in 207 patients without implantable cardioverter-defibrillator therapy was 23.2% and in 21 patients with implantable cardioverter-defibrillator therapy was 4.7%. In a Cox proportional hazards model for all 228 study patients (mortality while on the waiting list: 21.5%; transplantation rate: 54.8%), the absence of an implantable cardioverter-defibrillator was only a marginally significant predictor of mortality ($p = 0.079$). However, the absence of an implantable cardioverter-defibrillator was a powerful predictor of mortality for a subgroup of 134 patients with high-grade ventricular arrhythmias on Holter electrocardiography (mortality while on the waiting list: 26.1%; transplantation rate: 54.5%; $p = 0.022$) and for a subgroup of 58 survivors of sudden cardiac death (mortality while on the waiting list: 22.4%; transplantation rate: 56.9%; $p = 0.018$). Implantable cardioverter-defibrillator therapy can be strongly recommended in transplant candidates with a history of sudden cardiac death. Recommendations for an expanded, prophylactic use of implantable cardioverter-defibrillator therapy in heart transplant candidates cannot be given. (J THORAC CARDIOVASC SURG 1995; 110:532-9)

Michael Grimm, MD,^a Georg Wieselthaler, MD,^a Raymond Avanessian, MD,^a Georg Grimm, MD,^b Herwig Schmidinger, MD,^c Wolfgang Schreiner, PhD,^a Andrea Podcizek, MD,^d Ernst Wolner, MD,^a and Günther Laufer, MD, Vienna, Austria

Patients with severe heart failure who are registered for heart transplantation face a high risk of death from sudden cardiac death while on the waiting list, mainly because of ventricular tachyarrhythmias.¹⁻³ A recent multicenter trial showed that more than 40% of all deaths in patients on the waiting list are sudden in nature.¹

Implantable cardioverter-defibrillators (ICDs) were shown to reduce cardiac mortality in patients with impaired left ventricular function by prevention

of sudden cardiac death.⁴ In patients with an ejection fraction less than 30%, ICD therapy resulted in a 5-year actuarial freedom from sudden cardiac death of 89.9%.⁵ Availability of transvenous systems with biphasic shock delivery is a major advantage for the safety of this technique,⁶ and low surgical mortality at implantation and efficacy of ICD therapy in a series of transplant candidates were recently shown.^{7,8} These encouraging data and the difficulty in identifying those particular transplant candidates who are at risk for sudden cardiac death while on the waiting list⁹ have stimulated the discussion about an expanded use of ICD therapy as a prophylactic bridge to heart transplantation. However, general prophylactic ICD therapy with an approximately \$40,000 device in all patients registered for transplantation would cause an enormous burden on health care resources.⁸

The aim of this study was to investigate by a Cox proportional hazards model the impact of ICD therapy on the mortality in patients registered for heart transplantation. Furthermore, the im-

From the Department of Cardiothoracic Surgery^a and the Second Department of Internal Medicine,^c University of Vienna; the Second Department of Internal Medicine,^b Landeskrankenhaus Klagenfurt; and the Third Department of Internal Medicine,^d Wilhelminenspital, Vienna, Austria.

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Address for reprints: Michael Grimm, MD, Department of Cardiothoracic Surgery, University of Vienna, Währinger Gürtel 18-20; A-1090 Vienna, Austria.

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Table I. Baseline characteristics

	All study patients (n = 228)	Subgroup of patients with high-grade ventricular arrhythmias on Holter ECG (n = 134)	Subgroup of survivors of sudden cardiac death (n = 58)	Patients with ICD therapy (n = 21)
ICD therapy (%)	21 (9.2)	21 (15.7)	21 (36.2)	21 (100)
Age (yr)	52.7 ± 10.6	53.2 ± 10.6	55.5 ± 9.1	53.9 ± 9.7
Sex (male:female)	198:30	117:17	50:8	18:3
Cause of heart failure (Idiop:Isch,%)	138:90	80:34	31:27	12:9
NYHA class	3.2 ± 0.6	3.3 ± 0.5	3.3 ± 0.5	3.1 ± 0.5
Absence of sinus rhythm (%)	78 (34.2)	52 (38.8)	20 (34.5)	9 (40)
LVEF (%)	16.1 ± 6.9	15.6 ± 5.9	15.3 ± 6.5	16.7 ± 4.2
Cardiac index (L/min/m ²)	2.1 ± 0.5	2.1 ± 0.5*	2.2 ± 1.7	2.3 ± 0.4
CVP (mm Hg)	10.6 ± 4.5	11.4 ± 4.6	11.1 ± 5.0	10.7 ± 5.7
PVR (Wood units)	2.7 ± 1.5*	2.6 ± 1.4*	2.5 ± 1.7	1.8 ± 0.8
Antiarrhythmic drug at listing (%)	25 (11)*	21 (15.8)	14 (24.6)	6 (30)
Ventricular arrhythmia on Holter ECG (%)	134 (58.8)*	134 (100)	55 (94.8)	21 (100)

Values are expressed as mean value plus or minus the standard deviation or as a proportion. *Idiop*, Idiopathic heart failure; *Isch*, ischemic heart failure; *NYHA*, New York Heart Association; *LVEF*, left ventricular ejection fraction; *CVP*, central venous pressure; *PVR*, pulmonary vascular resistance.

**p* < 0.05 between patients with and without ICD therapy among all study patients and within both subgroups (for exact values see Results section).

Table II. Follow-up of patients on the waiting list

	All study patients (n = 228)	Subgroup of patients with high-grade ventricular arrhythmias on Holter ECG (n = 134)	Subgroup of survivors of sudden cardiac death (n = 58)	Patients with ICD therapy (n = 21)
Follow-up time (mo)*	11 (0.25-20)	11 (0.5-20)	11 (0.5-20)	11 (1-20)
Waiting time to transplantation (mo)†	4 (0.25-20)	4 (0.5-20)	4 (0.5-20)	4 (1-20)

Calculation of follow-up times and waiting times to transplantation derived from Kaplan-Meier analysis. Values are expressed as median and range. Starting point: registration on the waiting list.

*End point: still waiting at the end point of study.

†End point: transplantation.

pact of ICD therapy was calculated for the subgroup of patients with high-grade ventricular arrhythmias seen on Holter electrocardiography (ECG) and for the subgroup of patients who had already had an event of sudden cardiac death before registration.

Patients and methods

Baseline characteristics and follow-up. We reviewed the history of 228 consecutive heart transplant candidates registered by the transplant center of the University of Vienna, Austria, to the Eurotransplant waiting list between March 1, 1992 (starting point of the study: on this date the first patient with an ICD was registered), and October 31, 1993 (end point of the study). The indication for transplantation in all patients was end-stage heart disease, with unacceptable prognosis for survival and unacceptable disability even after careful consideration of all other medical and surgical therapy.¹⁰ All baseline character-

istics of study patients were recorded within 4 weeks before registration and are presented in Table I. Twenty-one out of the 228 patients were registered with ICD therapy, which was given for an event of ventricular tachyarrhythmia before registration that necessitated external electric defibrillation (median implantation time of the ICDs before registration: 6 months, range from 0.25 to 84 months).

While on the waiting list all patients were monitored clinically with comparable intensity. ICD function was monitored with respect to adequate discharges; ICD discharges were counted during follow-up while the patient was on the waiting list. At the time of registration for transplantation patients were treated with angiotensin-converting enzyme inhibitors (94.7%), digitalis (93.8%), diuretics (95.2%), antiarrhythmic drugs (11%; amiodarone *n* = 23 and sotalolol *n* = 22), and permanent anticoagulation therapy (77.5%). Intravenous catecholamines were administered in 11.5% and prostaglandins in 4% of the patients.

Follow-up times on the waiting list and waiting times to transplantation are presented in Table II.

Subgroups

Subgroup with high-grade ventricular arrhythmias on Holter ECG. In 134 patients (21 with and 113 without ICD therapy) high-grade ventricular arrhythmias (couplets/triplets and/or ventricular arrhythmias ≥ 4 consecutive complexes at a rate $\geq 120/\text{min}$) were present on Holter ECG, which was done within 4 weeks before registration.^{9, 11}

Subgroup of survivors of sudden cardiac death. Before registration for transplantation 58 patients (21 with and 37 without ICD therapy) had had an event of sudden cardiac death and were successfully resuscitated. Sudden cardiac death was classified by one or a combination of the following: the lack of worsening of the clinical setting within 1 hour before cardiac arrest, the need for external electric defibrillation for resuscitation, or ECG documentation of life-threatening ventricular arrhythmias.⁴ Documented rhythm during cardiac arrest was ventricular fibrillation in 36 patients (62%), ventricular tachycardia in 20 patients (34%), and unknown in 2 patients (4%). In the majority of the 37 patients without ICD therapy, ICD therapy was avoided for nonmedical reasons (costs, $n = 16$; referring centers refused use of ICDs, $n = 8$; ICD refused by the patient, $n = 5$) and in the minority of patients for medical reasons (worsening of the clinical setting after resuscitation, $n = 2$; intention to avoid thoracotomy in the elderly, $n = 2$; intention to await transplantation in the hospital, $n = 4$). Patients with ventricular tachyarrhythmias during an episode of pump failure or after a new Q wave myocardial infarction were not included in this subgroup.

Death on the waiting list: evaluation of circumstances.

For evaluation of circumstances of death that occurred while the patient was on the waiting list, personal or telephone contact was made with the physicians of the patients or their family members. Sudden cardiac death while on the waiting list was defined as death occurring as a result of recurrent cardiac arrest or within 1 hour of the development of symptoms in a patient previously in stable condition or an unobserved death in a patient known to be in stable condition during the preceding 24 hours. Pump failure death while a patient was on the waiting list was defined as death as a result of one or more of the following: progressive heart failure, recurrent myocardial infarction, or preceding symptoms of more than 1 hour.⁴ Unknown death while a patient was on the waiting list was defined as an event for which there was no knowledge about circumstances.

Statistical analysis. Comparisons between patients with and without ICD therapy were made by unpaired t test and χ^2 analysis; level of significance was set at $p \leq 0.05$.

In the Cox proportional hazards model, patients who did not die while on the waiting list were censored at the time of transplantation or at the last follow-up while on the waiting list at the end point of the study. Covariables used for calculation of independent predictors of mortality were the absence of ICD therapy and baseline characteristics (Table I). All variables that reached statistical significance in univariate analysis entered stepwise multivariate analysis. The estimation of relative risk and 95% confidence limits was calculated for each significant pre-

dictor from the proportional hazard model. Cox proportional model analysis was done with BMDP statistical software, 1990 version (BMDP Statistical Software, Inc., Los Angeles, Calif.).

Actuarial freedom from mortality while on the waiting list was calculated by Kaplan-Meier analysis with the use of SAS statistical software (SAS Institute Inc., Cary, N.C.).

Results

Baseline characteristics and follow-up. Detailed baseline characteristics of all study patients, of subgroups, and of patients with ICDs are presented in Table I.

All 228 study patients. Mean pulmonary vascular resistance was lower in the 21 patients with ICDs (1.8 Wood units) as compared with that in the 207 patients without ICDs (2.8 Wood units). High-grade ventricular arrhythmias on Holter ECG occurred more frequently in the 21 patients with ICDs (100%) as compared with the frequency in the 207 patients without ICDs (54.6%). Antiarrhythmic drug therapy was given to 6 of 21 patients with ICDs (30%), but only to 19 of 207 patients without ICDs (9.2%).

Subgroup of 134 patients with high-grade ventricular arrhythmias on Holter ECG. Mean cardiac index (2.3 L/min per square meter) and mean pulmonary vascular resistance (1.8 Wood units) were better in the 21 patients with ICDs as compared with respective values in the 113 patients without ICDs (mean cardiac index, 2.1 L/min per square meter; mean pulmonary vascular resistance, 2.7 Wood units).

Subgroup of 58 survivors of sudden cardiac death.

There was no difference in baseline characteristics between the 21 patients with and the 37 patients without ICDs.

In all 228 study patients and in the subgroups, follow-up times and waiting times to transplantation were comparable in patients with and without ICDs (Table II).

Outcome. Outcomes of all 228 study patients, of subgroups, and of patients with ICD therapy are presented in Table III.

The total mortality rate in all 228 study patients was 21.5%. Notably, within the whole study population and in the subgroup of patients with high-grade ventricular arrhythmias on Holter ECG sudden cardiac death occurred more frequently than death from pump failure. In the subgroup of survivors of sudden cardiac death, the most common event of death was pump failure. The mortality rate in 207

Fig. 1. Actuarial freedom from mortality in patients on waiting list. *Line 1*, 21 patients with ICD therapy; *line 2*, subgroup of survivors of sudden cardiac death ($n = 58$, including 21 patients with ICD therapy); *line 3*, all study patients ($n = 228$, including 21 patients with ICD therapy); *line 4*, subgroup of patients with high-grade ventricular arrhythmias on Holter ECG ($n = 134$, including 21 patients with ICD therapy).

Table III. Outcome

	All study patients ($n = 228$)	Subgroup of patients with high-grade ventricular arrhythmias on Holter ECG ($n = 134$)	Subgroup of survivors of sudden cardiac death ($n = 58$)	Patients with ICD therapy ($n = 21$)
Death while on the waiting list (%)	49 (21.5)	35 (26.1)	13 (22.4)	1 (4.7)
Sudden cardiac death (%)	28 (12.3)	19 (14.2)	6 (10.3)	—
Pump failure death (%)	20 (8.8)	15 (11.2)	7 (12.1)	1 (4.7)
Unknown cause of death (%)	1 (0.4)	1 (0.7)	—	—
Still on the waiting list (%)	54 (23.7)	26 (19.4)	12 (20.7)	6 (28.5)
Received transplantation (%)	125 (54.8)	73 (54.5)	33 (56.9)	14 (66.7)

patients without ICDs was 23.2% and the rate was 4.7% in 21 patients with ICDs.

The actuarial freedom from mortality while on the waiting list in all 228 study patients, subgroups, and patients with ICD therapy is shown in Fig. 1.

ICD discharges during follow-up while the patient was on the waiting list occurred in 17 (80.9%) of the 21 patients with ICDs. The median number of ICD discharges that occurred in those patients was 18.5 (range 1 to 370).

Cox proportional hazards model. The significant predictors of mortality while patients were on the waiting list, relative risk, and 95% confidence limits are presented in Table IV. All presented variables were statistically significant in univariate analysis.

All study patients ($n = 228$). Stepwise multivariate survival analysis revealed that mortality was most powerfully predicted by central venous pressure ($p < 0.0001$), cardiac index ($p = 0.002$), and the absence of sinus rhythm ($p = 0.035$). The absence of

Table IV. Multivariate predictors of mortality in patients on the waiting list (Cox proportional hazards model)

	<i>p</i> Value	Relative risk	95% confidence limits
All study patients (<i>n</i> = 228)			
CVP	<0.0001	1.1156	1.0698-1.1633
Cardiac index	0.002	0.4614	0.3257-0.6533
Absence of sinus rhythm	0.035	1.7655	1.3059-2.3866
Absence of ICD therapy	0.079	5.4229	1.9428-15.1515
Ventricular arrhythmias on Holter ECG	0.079	1.7695	1.2718-2.4618
Cause of heart failure	0.080	1.6745	1.2498-2.2434
Subgroup of patients with high-grade ventricular arrhythmias on Holter ECG (<i>n</i> = 134)			
Cardiac index	0.001	0.4769	0.3159-0.7199
CVP	0.014	1.1273	1.0701-1.1876
Absence of ICD therapy	0.022	5.1626	1.8467-14.4508
Absence of sinus rhythm	0.073	1.8810	1.3182-2.6823
Subgroup of survivors of sudden cardiac death (<i>n</i> = 58)			
Age	0.005	1.1286	1.0703-1.1900
Absence of ICD therapy	0.018	6.6533	2.3474-18.8679

Covariables used were baseline characteristics and the absence of ICD therapy (see Table I); all significant variables from univariate analysis entered stepwise multivariate analysis. CVP, Central venous pressure.

ICD therapy ($p = 0.079$), the presence high-grade ventricular arrhythmias on Holter ECG ($p = 0.079$), and the cause of heart failure ($p = 0.080$) were marginally significant independent predictors of mortality.

Subgroup of patients with high-grade ventricular arrhythmias on Holter ECG ($n = 134$). Death while patients were on the waiting list was strongly predicted by cardiac index ($p = 0.001$), central venous pressure ($p = 0.014$), and the absence of ICD therapy ($p = 0.022$), whereas the absence of sinus rhythm was only marginally predictive ($p = 0.073$).

Subgroup of survivors of sudden cardiac death ($n = 58$). Age ($p = 0.005$) and the absence of ICD therapy ($p = 0.018$) were significant independent predictors of mortality.

Antiarrhythmic therapy had no impact on mortality in patients on the waiting list for all 228 patients and subgroups.

Discussion

In the cohort of 228 unselected, consecutive heart transplant candidates, ICD therapy had no impact on mortality while the patients were on the waiting list. However, in 134 patients with high-grade ventricular arrhythmias on Holter ECG and, particularly, in 58 patients with a history of sudden cardiac death ICD therapy had a significant impact on mortality.

Within the study period 28 (12.3%) of 228 consecutive patients died of sudden cardiac death while on the waiting list. In the 21 patients with ICDs there was no single event of sudden cardiac death.

This suggests that the conventional indication for ICD therapy, that is, surviving an event of sudden cardiac death, seems ineffective to protect the entire population of heart transplant candidates.^{6,8} Despite the safety and efficacy of ICDs in transplant candidates,⁶⁻⁸ a more expanded, and therefore prophylactic, use of ICD therapy will remain a matter of discussion. The difficulties in identifying transplant candidates at risk for sudden cardiac death prospectively and the enormous cost (approximately \$40,000 per device) of ICD devices force the critical design of ICD prophylaxis in transplant candidates.

In the subgroup of 134 patients with high-grade ventricular arrhythmias on Holter ECG (including 21 patients with ICDs) ICD therapy had a significant impact on mortality. We observed a 14.2% rate of sudden cardiac deaths and an overall mortality rate of 26.1%. The presence of high-grade ventricular arrhythmias on Holter ECG in advanced heart failure is an accepted predictor of cardiac mortality.^{12,13} A significant association of couplets/triplets or nonsustained ventricular tachycardia with increased risk of sudden cardiac death in patients with heart failure was recently shown,^{14,15} however, this still remains a matter of discussion.¹⁶ High-grade ventricular arrhythmias may increase mortality by triggering life-threatening arrhythmias that either result in sudden cardiac death or in poorly tolerated hemodynamic compromise and deterioration because of pump failure.¹⁷ ICDs detect and immediately terminate ventricular arrhythmias and, therefore, may not only prevent sudden cardiac death but also death from arrhythmia-induced pump failure.¹⁷

Efficacy of ICD therapy in the termination of potential life-threatening arrhythmias is reflected in the high incidence of (median 18.5) adequate ICD discharges in 17 of our 21 patients with ICDs during our short follow-up period. Our findings indicate that patients with high-grade ventricular arrhythmias on Holter ECG comprise a subpopulation at certain risk of sudden cardiac death while on the waiting list. Because heart transplant candidates with inducible ventricular arrhythmia on electrophysiologic stimulation have a significantly higher prevalence of lethal arrhythmic events,¹⁸ expanded electrophysiologic stimulation could possibly be helpful in identifying patients who might receive potential benefit from prophylactic ICD bridge to transplantation. However, this has to be investigated by means of a prospective randomized study.

Although not previously reported, it was not surprising to us that ICD therapy dramatically decreased mortality in survivors of sudden cardiac death on the transplant waiting list. In this subgroup of 58 survivors of sudden cardiac death (including 21 patients with ICDs) we observed a 10.3% rate of sudden cardiac deaths and an overall mortality rate of 22.4%. Although in this subpopulation the risk of early recurrence of lethal arrhythmia is significant,¹⁹ in our series pump failure death (12.1%) occurred more frequently than sudden cardiac death (10.3%). In severity of heart failure the 21 patients with ICDs were comparable to the 37 patients without ICDs at the time of registration (Table I). However, mortality was strikingly lower in the ICD-treated patients with respect to sudden cardiac death and pump failure death. It can be doubted that all ICD discharges in 80.9% of our patients with ICDs (median 18.5, up to 370) treated ventricular tachycardias that were spontaneous in nature. Much more, follow-up on the waiting list revealed a marked correlation of ICD activity with worsening of ventricular function, as reported previously.^{5, 20} Therefore we speculate that the low number of pump failure deaths in our patients with ICDs does not mark patients with ICDs as "less sick," but we believe that immediate and consequent terminations of frequently occurring ventricular arrhythmias, which otherwise would have triggered hemodynamic deterioration, markedly supported prevention from pump failure death. ICD therapy was not given to 37 of the 58 survivors of sudden death, mainly because of nonmedical reasons such as cost or refusal of ICD therapy by referring medical centers. The approaches of awaiting transplantation under close Holter monitoring

out of the hospital and of awaiting transplantation in the hospital turned out not to be effective alternatives to ICD therapy. For this purpose, we believe that transplant candidates with a history of sudden cardiac death should receive ICD therapy whenever possible, even when waiting time to transplantation is expected to be short.

The major aim of ICD therapy while a patient is on the waiting list for heart transplantation is short-term survival until transplantation. Under the assumptions of further limited availability of donor organs and a decreased mortality with prophylactic ICD therapy, waiting times to transplantation and time-dependent risk of deterioration caused by pump failure will increase for the patients. An overrepresentation of ICD therapy in transplant candidates will result in a great pool of patients with critical end-stage disease with severe pump failure,⁵ which would finally negatively affect the outcome of the entire transplant program by increased perioperative mortality after transplantation.²¹ Further studies will be necessary to evaluate which percentage of patients listed with ICD therapy optimizes overall survival for patients on the waiting list, without significant disadvantages for patients listed without ICDs. Therefore too enthusiastic use of prophylactic ICD therapy should be avoided. To optimize the cost-benefit ratio of short-term ICD bridge to transplantation, technology will have to focus on cheaper, simpler, or reusable devices. It seems likely that empiric use of amiodarone and sotalol in patients who are heart transplant candidates would be cheaper than ICD therapy and more suitable for expanded prophylaxis of lethal arrhythmias.²² Studies on empiric use of amiodarone in advanced heart failure report effective suppression of ventricular arrhythmias; unfortunately this beneficial effect did not necessarily correlate with increased survival.^{23, 24} As we calculated in multivariate analysis, therapeutic, that is, nonempiric, use of antiarrhythmic therapy with sotalol and amiodarone had no impact on mortality. It is hoped that ongoing work within the Congestive Heart Failure Survival Study of Antiarrhythmic Therapy will help to determine benefit from prophylactic antiarrhythmic therapy.²⁵

The study is limited by its retrospective design and the fact that ICD therapy was not randomly assigned. Another major bias was that the low number of patients with ICD therapy resulted in discrepancy of sample sizes within the groups. The latter and differences in baseline characteristics of patients

with and without ICDs were corrected for influencing factors by the Cox model used. Another potential source of undetected bias is the high number of referring centers, which results in a variety of approaches toward prevention and treatment of life-threatening ventricular arrhythmias. Another limitation of this study is the inability to exactly discriminate between tachyarrhythmia and electromechanical dissociation as the rhythm at the time of sudden cardiac arrest.²⁶ Finally, it has to be stated that this study only focused on a few months of events in patients on the heart transplant waiting list. Therefore the conclusions drawn in this study should not be extrapolated to long-term outcome of patients with heart failure.

We conclude that ICD therapy should be given, whenever possible, to heart transplant candidates with a history of sudden cardiac death before registration. For all other transplant candidates no recommendations for prophylactic ICD bridge to transplant can be made. However, further studies should clarify whether vigorous electrophysiologic stimulation in patients with high-grade ventricular arrhythmias on Holter ECG is helpful in identifying transplant candidates at risk for sudden cardiac death on the waiting list.

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