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ORIGINAL ARTICLE

Primary preventive cardioverter-defibrillator implantation (Pro-ICD) in patients awaiting heart transplantation. A prospective, randomized, controlled 12-year follow-up study

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Summary

The aim of this study was to evaluate whether short-term primary preventive cardioverter-defibrillator (ICD) implantation as bridge to heart transplantation (HTX) provides any survival benefit. Thirty-three patients awaiting HTX were randomized to either conventional therapy (control group) or primary preventive ICD implantation (ICD group). Fourteen patients had ischemic cardiomyopathy (ICM) and 19 patients had dilated cardiomyopathy (DCM). Sixteen patients were randomized to the ICD group and 17 patients were randomized to the control group. Twenty patients (61%) were transplanted after a waiting time of 10 ± 9 months. The remaining 13 patients (39%) were not transplanted because of clinical improvement (n = 5), cerebral hemorrhage (n = 3), or death (n = 5). On the waiting list, 3 ICD patients with DCM developed slow VTs without ICD intervention, two patients with ICM (6%) had fast VT terminated by the ICD, and no arrhythmic death was observed. After 11.9 years (median), 13 of 20 HTX patients (65%) and 5 of 13 non-HTX patients (38%) were alive. Survivors had a higher LVEF (22 ± 6 vs. 17 ± 4%, P = 0.0092) and a better exercise capacity (75 ± 29 vs. 57 ± 24 Watt, P = 0.0566) at baseline as compared to nonsurvivors. This study may not support the general use of primary preventive ICDs as a short-term bridge to heart transplantation.

Introduction

Poor left ventricular (LV) function is considered the most important predictor of total cardiac mortality [1]. Patients on the waiting list for heart transplantation (HTX) have a clinical profile, which meets current guidelines for primary preventive cardioverter-defibrillator (ICD) implantation [2]. In retrospective studies, ICD therapy has been shown to effectively reduce sudden cardiac death in patients with severe LV dysfunction awaiting HTX [3–5]. However, to date, there are no prospective, randomized, controlled data available demonstrating that in the short-term primary preventive ICD implantation as bridge to HTX provides any survival benefit. Long-term results from large prospective primary preventive ICD trials [6,7] may not be applied to the short-term setting of patients awaiting HTX.

Therefore, the primary goal was to prospectively compare all-cause mortality and arrhythmic mortality between the two treatment arms (ICD vs. control). Secondary goals were clinical and nonclinical parameters, which may provide important prognostic information regarding patients' outcome.

Patients and methods

Study design and study population

This was an open, prospective, randomized, controlled (Phase II) study performed at the Medical University of Vienna. Consecutive patients placed on the "Eurotrans-

plant" waiting list for cardiac transplantation were enrolled from July 2000 through January 2002. The study was planned to enroll 100 patients over a period of 2 years. However, the recruitment rate was lower than expected and 33 patients were included. Eligible patients were randomized to either conventional therapy (control group) or to ICD implantation on the top of conventional therapy (ICD Group). All patients gave their written consent. The local ethics committee approved the active phase of this study (time on the waiting list) and the subsequent 12-year follow-up period. Follow-up was closed in March 2014.

Inclusion and exclusion criteria

Inclusion criteria are as follows: on waiting list for heart transplantation ($\leq$ 4 weeks), history of manifest right or left ventricular heart failure, NYHA class III/IV, VO_2 max $\leq$ 14 ml/kg/min on spiro-exercise stress testing, and optimized medical therapy since at least 1 month. Exclusion criteria are as follows: age $\leq$ 18 years, history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), history of cardiac arrest, history of syncope and inducible VT/VF on EP study after enrollment on waiting list, mechanical tricuspid heart valve, pacemaker implanted or indicated, ICD or left ventricular assist device implanted, participation in another clinical trial, and pregnancy at the time of enrollment.

Examinations and devices

The severity of mitral regurgitation was evaluated semiquantitatively from the area of the regurgitant jet by color Doppler. Left ventricular ejection fraction was calculated from radionuclide angiography. Twenty-four-hour Holter monitoring for HRV with SAECG was performed. Time-domain analysis was obtained in each patient using a band-pass filter at 25–250 Hz. Four hundred and fifty to 600 beats were averaged (noise level<0.5 A V). Late potentials were present according to recommendations [8]. The standard deviation of all normal-to-normal R–R intervals (SDNN) was chosen for HRV. In all patients randomized to ICD therapy, the unipolar Medtronic single chamber ICD model 7223Cx was used. The device can detect episodes of ventricular tachycardia (VT), fast ventricular tachycardia (FVT), or ventricular fibrillation (VF) and, upon detection, deliver the programmed pacing, cardioversion, or defibrillation therapies.

Endpoints and classification of death

The primary endpoint was all-cause mortality. A secondary composite endpoint was all-cause mortality and virtual mortality (fast VT/VF terminated by ICD shock). Further secondary endpoints were parameters obtained by ECG, Holter, and echocardiographic investigation. Deaths were categorized utilizing an adapted form of the Hinkle classification [9] in cardiac and noncardiac (NC) and attributed with sudden arrhythmic or nonsudden incidence (NSC). Slow VT was defined as VT with a cycle length above 400 ms (150 bpm). VT was defined as VT with a cycle length between 400 and 250 ms (150–240 bpm). Fast VT/VF was defined as ventricular tachyarrhythmia with a cycle length below 250 ms (240 bpm). VF or VT >240 bpm leading to syncope before ICD therapy and multiple VT episodes (electrical storm) leading to syncope and ICD discharge without ICD therapy-related acceleration were taken as surrogate for sudden arrhythmic death [10]. All other ICD therapies without syncope or because of VT <240 bpm were not taken as surrogate for sudden arrhythmic death.

Statistical analysis

Mean $\pm$ standard deviation is shown for metric variables and absolute frequencies (relative frequencies within a column) for categorical variables. Between-group comparisons were performed using *t*-tests or chi-squared tests as appropriate. Kaplan–Meier survival curves were constructed for ICD group and control group. Death is considered as event and patients, if they were transplanted, were censored at the date of the transplantation. The analysis of the active phase (30 months) encompasses a log-rank test for the difference in the distribution of survival in both groups and a significance test in the difference in restricted mean survival time. A log-rank test for a comparison of the distribution of overall survival between ICD and control group was calculated. To adjust the analysis of the effect of ICD on overall survival for possible confounders, a multiple Cox regression was fitted. Age, type of cardiomyopathy, LV ejection fraction, antiarrhythmic drugs, heart rate variability, and exercise capacity were considered as potential confounders. A stepwise backward selection algorithm using the Bayesian information criterion was applied. Age and LV ejection fraction were selected and were thus included in the final model together with ICD. *P*-values of 0.05 or less were considered to be statistically significant. The analyses of secondary endpoints are regarded as descriptive. All calculations were performed in R 3.0.2. R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Results

This study includes baseline and follow-up data (median 11.9 years) of 33 patients (94% males, aged 53 $\pm$ 9, range

34–65 years) listed for heart transplantation who were randomized to ICD or conventional therapy. Patients' clinical characteristics are summarized in Table 1, column "Total." Fourteen patients had ischemic cardiomyopathy (ICM) and 19 patients had dilated cardiomyopathy (DCM). The mean time from diagnosis of cardiomyopathy to study inclusion was 5.6 ± 4.4 years. Patients with ICM had a borderline significant lower LVEF as compared to DCM patients ($P = 0.0482$). The most frequent comorbidity was hypertension (70%). There was a high rate of cigarette smoker (85%). Most patients had moderate mitral regurgitation (73%). Sixteen patients (49%) were randomized for ICD therapy on the top of conventional therapy (ICD group) and 17 patients (51%) were randomized for conventional therapy only (control group). The mean time to HTX was 10 ± 9 months. Twenty patients (61%) were transplanted.

Table 2 highlights patients' characteristics and follow-up results according to the HTX status. HTX patients had a lower maximal aerobic capacity (7.6 ± 1.8 vs. 9.1 ± 1.4 ml/min/kg), but higher PAP (35.9 ± 8.1 vs. 28.2 ± 8.2 mm Hg), PCWP (24.8 ± 5.7 vs. 19.8 ± 7.1 mm Hg), and Wood values (3.1 ± 1.3 vs. 2.1 ± 0.7 mm Hg/l/min) as compared to patients not undergoing HTX. The study flowchart (Fig. 1) demonstrates the outcomes according to randomization "ICD" versus "no-ICD." In the ICD group, patients with DCM developed slow VT episodes in 3 cases, whereas fast VT/VF was seen in two ICM patients (6%). All VT episodes occurred on the waiting list for HTX. There was no arrhythmic death because of VT/VF in the "no-ICD" group. The study flowchart demonstrates the further clinical history of the patients depending upon HTX was performed or not. The resulting survival status and classification of death are outlined in Fig. 1: There

Table 1. Clinical stratified according to the type of cardiomyopathy.

	Total $n = 33$	ICM $n = 14$	DCM $n = 19$	P for trend
Baseline characteristics				
Age, years	53 ± 9	52 ± 7	54 ± 10	0.6923
Male	31 (94)	12 (86)	19 (100)	0.0945
Body mass index	26 ± 4	26 ± 3	26 ± 4	0.7846
Known cardiomyopathy, years	5.6 ± 4.4	4.5 ± 4.2	6.4 ± 5.2	0.2058
LV ejection fraction, %	19 ± 6	17 ± 4	21 ± 6	0.0482
RV ejection fraction, %	22 ± 10	19 ± 9	23 ± 11	0.28
QRS width, ms	134 ± 27	135 ± 27	134 ± 27	0.9719
ICD randomized	16 (49)	8 (57)	8 (42)	0.4088
Comorbidities				
Hyperlipidemia	10 (30)	8 (57)	2 (11)	0.003
Hypertension	23 (70)	10 (71)	13 (68)	0.8582
Cigarette smoker	28 (85)	14 (100)	14 (74)	0.038
Alcohol intake	13 (39)	6 (43)	7 (37)	0.7366
Medication				
ACE-inhibitors/ARBs	33 (100)	14 (100)	19 (100)	0.3841
Diuretics	17 (52)	9 (64)	8 (42)	0.3641
Spironolactone	16 (48)	5 (36)	11 (58)	0.3641
B-blocker	27 (82)	12 (86)	15 (79)	0.614
Amiodarone	8 (24)	2 (14)	6 (32)	0.2658
Digitalis	22 (67)	9 (64)	13 (68)	0.8107
Nitrates	3 (9)	3 (21)	0	0.0349
Statins	15 (45)	14 (100)	1 (5)	<0.0001
Prostaglandin pump	10 (30)	5 (36)	5 (26)	0.5757
Others				
Blood creatinine, mg/dl	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.2	0.9113
Blood urea nitrogen, mg/dl	26.7 ± 35.9	32.8 ± 55.1	22.1 ± 7.2	0.4075
Cardiothoracic ratio	0.6 ± 0.1	0.6 ± 0.0	0.6 ± 0.1	0.9756
Echo				
LV enddiastolic diameter, mm	70.7 ± 10.1	74.0 ± 10.7	68.3 ± 9.2	0.1088
Mild mitral regurgitation	7 (21)	4 (29)	3 (16)	0.3905
Moderate mitral regurgitation	24 (73)	10 (71)	14 (74)	0.89
Severe mitral regurgitation	2 (6)	0	2 (11)	0.2229
Mild tricuspid regurgitation	12 (36)	4 (29)	8 (42)	0.4403
Moderate tricuspid regurgitation	15 (46)	8 (57)	7 (37)	0.2608
Severe tricuspid regurgitation	1 (3)	0	1 (5)	0.3992

Table 2. Clinical data stratified according to the status of HTX.

	Total $n = 33$	HTX $n = 20$	No HTX $n = 13$	P for trend
Baseline characteristics				
Age, years	53 ± 9	53 ± 9	53 ± 10	0.8993
Male	31 (94)	19 (95)	12 (92)	0.7606
Body mass index	26 ± 4	26 ± 3	28 ± 4	0.1026
LV ejection fraction, %	19 ± 6	19 ± 6	20 ± 6	0.9081
RV ejection fraction, %	22 ± 10	21 ± 10	22 ± 11	0.6901
ICD randomized	16 (49)	12 (60)	4 (31)	0.1069
Ventilation/Hemodynamics				
Exercise capacity, Watt	67 ± 28	66 ± 30	69 ± 27	0.7416
VO2 basal, ml/min/kg	4.2 ± 0.8	4.2 ± 0.7	4.1 ± 0.9	0.8412
VO2 maximal capacity, ml/min/kg	8.3 ± 1.8	7.6 ± 1.8	9.1 ± 1.4	0.0258
VO2 peak consumption, ml/min/kg	10.7 ± 2.5	10.2 ± 2.4	11.6 ± 2.5	0.1184
Heart rate, beats/min	80 ± 20	74 ± 18	87 ± 22	0.083
Pulmonary artery pressure, mm HG	32.8 ± 8.9	35.9 ± 8.1	28.2 ± 8.2	0.012
PCWP, mm HG	22.9 ± 6.6	24.8 ± 5.7	19.8 ± 7.1	0.0378
Cardiac output, l/min	4.1 ± 0.9	4.0 ± 0.9	4.3 ± 0.9	0.2813
Cardiac index, l/min/m^2	2.1 ± 0.4	2.0 ± 0.4	2.2 ± 0.4	0.2046
Stroke volume, ml	54 ± 17	54 ± 15	54 ± 20	0.9811
Stroke index, ml/m^2	27 ± 8	27 ± 8	26 ± 9	0.7772
WOOD, mm HG/l/min	2.7 ± 1.2	3.1 ± 1.3	2.1 ± 0.7	0.027
Sinus rhythm	25 (76)	16 (80)	9 (69)	0.496
Nonsustained VT	17 (52)	10 (50)	7 (54)	0.8354
QTc (Bazett), ms	444 ± 85	441 ± 104	449 ± 44	0.7958
Heart rate variability, SDNN	85 ± 32	84 ± 31	87 ± 36	0.8386
SAECG positive	13 (39)	7 (35)	6 (46)	0.5366
Nonsudden cardiac death	7 (21)	2 (21)	5 (39)	0.0527
Noncardiac death	8 (24)	4 (20)	4 (31)	0.496
Survival time, years	8.3 ± 5.6	10 ± 4.9	5.5 ± 5.5	0.0211

Data are presented in *n* (%) when not otherwise indicated.

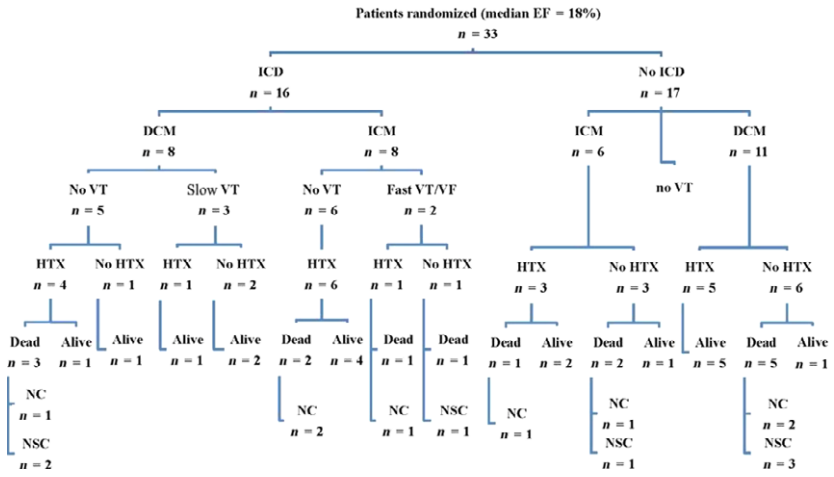

Figure 1 Procedural flowchart. Outcomes of 33 patients randomized for ICD or conventional therapy. Stratification according the underlying heart disease: DCM=dilated cardiomyopathy and ICM=ischemic cardiomyopathy. Number of VT event in the ICD group. There were no VT/VF or syncope events in the no-ICD group. Further stratification according to heart transplantation or not and finally modalities of death. VT=ventricular tachycardia, NC=noncardiac death, NSC=nonsudden cardiac death.

were only noncardiac (NC) and nonsudden cardiac deaths (NSC). There was no arrhythmic death. Twenty patients were transplanted. Thirteen patients (39%) were not transplanted because of clinical improvement (four patients), cerebral hemorrhage (three patients), or death (six patients): three ICM patients on the waiting list and three

DCM patients after the removal from the waiting list because of cerebral hemorrhage, acute heart failure with LVAD implantation, or renal failure. The death rate for patients initially listed for HTX until HTX was 18%. When taking a 14-day perioperative window into account, nine patients (27%) died in the active study phase (three patients died shortly after HTX). At the end of follow-up, 14 of 20 (70%) of HTX patients and 4 of 13 (31%) of non-HTX patients were alive. The resulting survival time was significantly longer in patients undergoing HTX as compared to patients not undergoing HTX (10 ± 5 vs. 6 ± 6 years, $P = 0.0211$, Table 2). Details about survival status, baseline, and follow-up data are listed in Table 3. Patients who survived had a higher LVEF (22 ± 6 vs. 17 ± 4%), a better exercise capacity (75 ± 29 vs. 57 ± 24 Watt), and a higher HRV (96 ± 27 vs. 72 ± 35 SDNN) at baseline as compared to patients who died.

Figure 2a demonstrates that short-term all-cause mortality until HTX ($P = 0.191$) and long-term all-cause mortality were not dependent on primary preventive ICD implantation ($P = 0.1286$). The restricted mean in the ICD group and control group at 30 months was 26.5 months and 20.9 months, respectively. The test in restricted mean difference was not significant ($P = 0.2078$). When taking also ICD aborted fast VT/VF episodes (virtual mortality) into account (Fig. 2b), short-term mortality until HTX ($P = 0.5267$) and long-term mortality were not dependent on primary preventive ICD implantation ($P = 0.7682$). Results from a multivariate Cox regression analysis are shown in Table 4. Age and LVEF were selected as predictors for overall survival. However, similar to the unadjusted analysis, no significant effect of ICD randomization on survival was fond ($P = 0.1754$).

Discussion

This is the first study providing short- and long-term data from randomized, primary preventive implantation of ICDs in patients on the waiting list for heart transplantation. The major finding of this study is that life-threatening VT episodes occur less frequently than anticipated suggesting reconsideration of primary preventive implantation of defibrillators in this setting.

Current guidelines assign a class IIa (level of evidence C) recommendation for primary preventive ICD implantation in patients on the waiting list for heart transplantation. In contrast, ICD implantation is not recommended for

Table 3. Clinical data stratified according the status of survival.

	Total $n = 33$	Alive $n = 18$	Dead $n = 15$	P for trend
Baseline characteristics				
Age, years	53 ± 9	53 ± 9	53 ± 8	0.9105
Male	31 (94)	18 (100)	13 (87)	0.1169
Body mass index	26 ± 4	26 ± 4	27 ± 4	0.6452
LV ejection fraction, %	19 ± 6	22 ± 6	17 ± 4	0.0092
RV ejection fraction, %	22 ± 10	23 ± 11	20 ± 10	0.3770
ICD randomized	16 (49)	9 (50)	7 (47)	0.8544
Ventilation/Hemodynamics				
Exercise capacity, Watt	67 ± 28	75 ± 29	57 ± 24	0.0566
VO2 basal, ml/min/kg	4.2 ± 0.8	4.1 ± 0.6	4.2 ± 0.9	0.7801
VO2 aerobic threshold, ml/min/kg	8.3 ± 1.8	8.2 ± 2.1	8.4 ± 1.1	0.7083
Peak VO2, ml/min/kg	10.7 ± 2.5	11.1 ± 2.6	10.2 ± 2.3	0.3238
Heart rate, beats/min	79 ± 20	75 ± 21	85 ± 19	0.1545
Pulmonary artery pressure, mm HG	33 ± 9	32 ± 9	34 ± 9	0.6368
PCWP, mm HG	23 ± 7	23 ± 7	23 ± 7	0.7122
Cardiac output, l/min	4.1 ± 0.9	4.0 ± 0.9	4.2 ± 0.9	0.7057
Cardiac index, $l*min^{-1}*m^{-2}$	2.1 ± 0.4	2.1 ± 0.5	2.1 ± 0.4	0.9298
Stroke volume, ml	54 ± 17	55 ± 15	52 ± 19	0.6472
Stroke index, ml/m^2	27 ± 8	28 ± 8	26 ± 9	0.5162
WOOD, mm HG/l/min	2.7 ± 1.2	2.6 ± 1.2	2.9 ± 1.2	0.5320
Sinus rhythm	25 (76)	13 (72)	12 (80)	0.6170
Nonsustained VT	17 (52)	8 (44)	9 (60)	0.3891
QTc (Bazett), ms	444 ± 85	430 ± 106	461 ± 45	0.2891
Heart rate variability, SDNN	85 ± 32	96 ± 27	72 ± 35	0.0396
SAECG positive	13 (39)	6 (33)	7 (47)	0.4509
Nonsudden cardiac death	7 (21)	0	7 (47)	0.0006
Noncardiac death	8 (24)	0	8 (53)	0.0001
Survival time, years	8.3 ± 5.6	12.8 ± 1.2	2.8 ± 2.8	<0.0001

Data are presented in *n* (%) when not otherwise indicated.

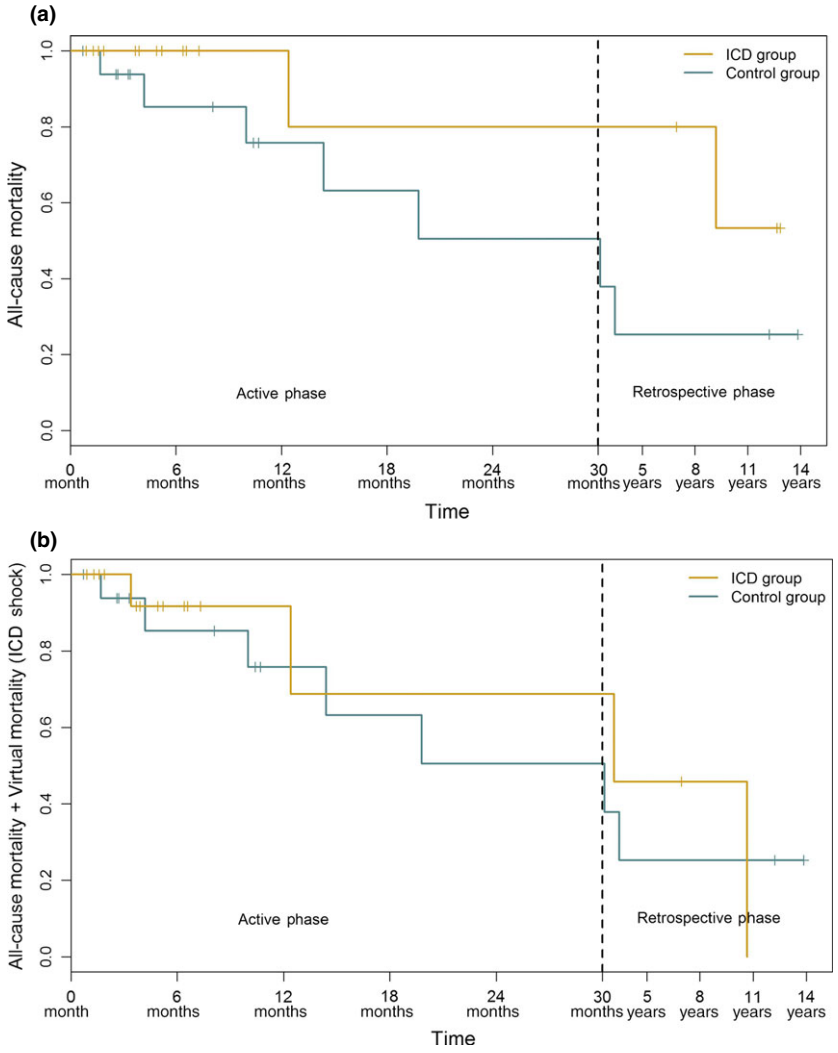

Figure 2 Time-to-death distribution. Stratification according to treatment: ICD group versus control group. The time axis is differently scaled after 30 months (indicated by the dotted line). (a) Kaplan–Meier estimate for all-cause mortality. The log-rank test for the difference in the distribution of survival times was neither for the active phase ($P = 0.191$) nor for the total observation time ($P = 0.1286$) significant. (b) Kaplan–Meier estimate for the composite endpoint of all-cause mortality and virtual mortality (fast VT/VF terminated by ICD shock). There was no significant difference between the two groups.

Table 4. Hazard ratio (HR) and 95% confidence intervals (CI) estimated from the multiple Cox regression model for overall survival.

	HR	Lower CI	Upper CI	*P*-value
Age (years)	1.09	0.99	1.2	0.0668
LV ejection fraction (%)	0.85	0.73	0.98	0.0286
ICD randomization	0.27	0.04	1.79	0.1754

patients without an expectation of survival with acceptable functional status for at least 1 year [11]. Randomized trials with end-stage heart failure patients listed for HTX are currently not available. Thus, recommendations on primary preventive ICD implantation in these patients are solely based on expert's expertise (level C) [6,7,11–13].

All available studies are retrospective studies including patients with a combination of primary and secondary or even unknown indication for ICD implantation. Sandner *et al.*[14]. demonstrated in ICD patients listed for HTX (12% of all patients) a survival benefit; however, no information was provided on whether the decision to implant an ICD was based on primary or secondary prevention indication. In the studies by Ermis *et al.*[15], Saba *et al.* [16], and Fröhlich *et al.* [17], 18–51% of the patients on the waiting list had ICDs implanted for primary and secondary sudden death prevention. In all studies, a substantial survival benefit was reported for ICD patients. In contrast, in the present prospective, randomized study, none of the patients had

a history of fatal ventricular arrhythmias. Of note, all deaths on the waiting list (12%) were noncardiac or nonsudden cardiac. Only two patients in the ICD group (6%) experienced fast and potentially life-threatening ventricular arrhythmias with syncope. Our findings are in good agreement with data by Da Rosa *et al.* [18] who reported a sudden death rate of only 2.5% of patients listed for HTX. In contrast, van den Broek *et al.* [19] report on a sudden death rate of at least 17% in patients on the HTX waiting list.

Sudden cardiac death is often defined as death within one hour after onset of acute symptoms or even unwitnessed, unexpected death in a patient known to have been stable within the previous 24 h [14,18,19]. In our study, we applied a clear discrimination between nonsudden cardiac and sudden arrhythmic death (death from fast ventricular arrhythmias). This difference in the definition of the mode of death may explain the low sudden arrhythmic death rate in the present study.

ICD therapy has been shown to effectively reduce sudden cardiac death in patients with severe LV dysfunction [20,21]. The vast majority of patients on the waiting list for HTX fulfill the criteria for primary or secondary ICD implantation. However, the time frame during which the implanted device potentially may save lives is rather short. In good accordance with other centers [17], the median waiting time to HTX in our center is 10 $\pm$ 9 months only. The low number of arrhythmic events suggests that long-term survival data as published in the primary prevention studies MADIT II [6] and SCD-HeFT [7] cannot be translated 1:1 to the short-term setting in patients awaiting HTX. In clinical practice, ICD implantation in patients on the waiting list for HTX varies between 5.5% [22] and 57% [23]. Considering the relative low risk of fatal arrhythmias, wearable cardioverter-defibrillators may be used in this patient setting as recently suggested [24].

Finally, after 12 years of follow-up, 65% of HTX patients are alive, whereas only 39% of patients without HTX have survived. This result emphasizes the benefit of HTX in patients with end-stage heart failure.

Limitations

The present single-center, open, prospective, randomized, controlled (Phase II) study had limitations. The sponsoring company prematurely stopped the study because the anticipated number of study patients (n = 100) was not reached in time. Therefore, the power to detect a true alternative hypothesis may be reduced and any finding should be labeled as pilot study results.

Conclusion

We observed a low risk of dying from ventricular arrhythmias in patients on the waiting list for heart transplantation. Thus, bridging patients on the waiting list with primary prophylactic ICDs may be reconsidered.

Authorship

TP and HS: designed the study. TP, MG, Laufer and HS: performed the study. TP, MG, FTM, GL and HS: collected the data. TP, HS, RR and DK: analyzed the data. TP and HS: wrote the paper. All authors are contributed in paper writing.

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