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Benefit of Combined Resynchronization and Defibrillator Therapy in Heart Failure Patients With and Without Ventricular Arrhythmias

Claudia Ypenburg, MD, Lieselot van Erven, MD, PhD, Gabe B. Bleeker, MD, Jeroen J. Bax, MD, PhD, Marianne Bootsma, MD, PhD, Maurits C. Wijffels, MD, PhD, Ernst E. van der Wall, MD, PhD, Martin J. Schalij, MD, PhD

Leiden, the Netherlands

OBJECTIVES We attempted to assess the efficacy of combined cardiac resynchronization therapy-implantable cardioverter-defibrillator (CRT-ICD) in heart failure patients with and without ventricular arrhythmias.

BACKGROUND Because CRT and ICDs both lower all-cause mortality in patients with advanced heart failure, combination of both therapies in a single device is challenging.

METHODS A total of 191 consecutive patients with advanced heart failure, left ventricular ejection fraction <35%, and a QRS duration >120 ms received CRT-ICD. Seventy-one patients had a history of ventricular arrhythmias (secondary prevention); 120 patients did not have prior ventricular arrhythmias (primary prevention). During follow-up, ICD therapy rate, clinical improvement after 6 months, and mortality rate were evaluated.

RESULTS During follow-up (18 ± 4 months), primary prevention patients experienced less appropriate ICD therapies than secondary prevention patients (21% vs. 35%, $p < 0.05$). Multivariate analysis revealed, however, no predictors of ICD therapy. Furthermore, a similar, significant, improvement in clinical parameters was observed at 6 months in both groups. Also, the mortality rate in the primary prevention group was lower than in the secondary prevention group (3% vs. 18%, $p < 0.05$).

CONCLUSIONS As 21% of the primary prevention patients and 35% of the secondary prevention patients experienced appropriate ICD therapy within 2 years after implant, and no predictors of ICD therapy could be identified, implantation of a CRT-ICD device should be considered in all patients eligible for CRT. (J Am Coll Cardiol 2006;48:464–70) © 2006 by the American College of Cardiology Foundation

Despite significant advances in the treatment of congestive heart failure (HF), the 5-year mortality exceeds 50% (1,2). Although the cause of death is HF-related in most patients with advanced symptoms, a significant proportion will die suddenly and unexpectedly due to ventricular arrhythmias.

Cardiac resynchronization therapy (CRT) in New York Heart Association (NYHA) functional class III and IV patients, with a wide QRS complex and depressed left ventricular (LV) function, has a positive effect on functional status, quality of life, and LV function as demonstrated by various randomized and non-randomized studies (3–7). Furthermore, the CARE-HF (Cardiac Resynchronization-Heart Failure) study reported a positive effect of CRT on all-cause mortality, as compared with optimal medical treatment alone (8). However, CRT alone will have a limited effect on the arrhythmic death rate.

Implantable cardioverter-defibrillators (ICD) provide a substantial mortality benefit by preventing sudden cardiac death in patients with previous ventricular arrhythmias (9). Furthermore, the SCD-HeFT (Sudden Cardiac Death in Heart Failure) trial showed that low left ventricular ejection fraction (LVEF) patients without ventricular arrhythmias, regardless of the underlying cause, benefit from an ICD on top of optimal medical therapy (10).

However, whether a combined CRT-ICD device should be implanted in all CRT candidates is still a matter of debate. The randomized COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) trial showed a trend for CRT only to decrease mortality, but reported a significant mortality effect in patients treated with a CRT-ICD device (11).

The aim of this study was to evaluate the number of ICD therapies in patients eligible for CRT with and without prior ventricular arrhythmias, who received a combined CRT-ICD device, and whether predictors of ventricular tachycardia (VT)/ventricular fibrillation (VF) could be determined. Secondary end points were response to CRT and mortality differences in patients with and without prior ventricular arrhythmias.

METHODS

Patients. From January 2000 to April 2004, all 195 consecutive patients eligible for CRT-ICD in our center were

From the Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands. This work was supported the Dutch Heart Foundation, grant no:2002B109.

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Abbreviations and Acronyms

ATP	= antitachycardia pacing
CI	= confidence interval
CRT	= cardiac resynchronization therapy
HF	= heart failure
HR	= hazard ratio
ICD	= implantable cardioverter-defibrillator
LV	= left ventricle/ventricular
LVEF	= left ventricular ejection fraction
NYHA	= New York Heart Association
VF	= ventricular fibrillation
VT	= ventricular tachycardia

included in this prospective analysis. Standard therapy guidelines were applied to indicate ICD implantation (12,13). Eligibility for CRT was based on the following criteria: 1) advanced HF (NYHA functional class III or IV); 2) LVEF <35%; and 3) wide QRS complex (>120 ms) with a left bundle branch pattern on the electrocardiogram.

Patients with ischemic as well as non-ischemic dilated cardiomyopathy were included. The etiology was considered ischemic in the presence of an old myocardial infarction and/or significant coronary artery disease (>50% stenosis in 1 of the major epicardial coronary arteries) on coronary angiography, whereas patients with normal coronary arteries were classified as non-ischemic. All patients underwent coronary angiography before implant. Patients with atrial fibrillation or previous implanted pacemakers were also included in this analysis.

The study protocol was as follows. Before implant patients were allocated to 1 of 2 groups according to the indication for ICD implantation: 1) CRT-ICD insertion was considered a primary preventive intervention in patients without life-threatening sustained ventricular arrhythmias. Patients with non-sustained VT on Holter monitoring or syncope without inducible ventricular arrhythmias during electrophysiological testing were also included in this primary prevention group; 2) CRT-ICD implantation was considered a secondary preventive intervention in sudden cardiac arrest survivors or in patients with sustained hemodynamic unstable VT, as well as in patients with syncope and inducible ventricular arrhythmia at electrophysiological testing (secondary prevention group).

For this analysis, follow-up was obtained up to 2 years. The ICD printouts were obtained every 3 months. Clinical evaluation was assessed at baseline and after 6 months, and thereafter at regular intervals.

CRT-ICD implantation. A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead into 1 of the posterolateral veins through an 8-F guiding catheter (Easytrak 4512-80, Guidant Corp., St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual-chamber biventricular ICD (Contak CD or Renewal, Guidant Corporation; Insync-III or Marquis, Medtronic Inc).

Procedural success was accomplished when pulse generator and the 3 leads were positioned without complications and biventricular pacing could be installed.

ICD evaluation. During follow-up, ICD printouts were obtained every 3 months. From these printouts, the incidence and type of arrhythmias, as well as the incidence of appropriate and inappropriate shocks, was determined. Shocks or antitachycardia pacing (ATP) were classified as appropriate when they occurred in response to VT or VF and as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction. Cutoff rate of the monitor or first therapy zone was noted.

Clinical evaluation. All patients were evaluated at the outpatient clinic at baseline and at 6 months after CRT-ICD implantation. Heart failure symptoms were classified using the NYHA score. Quality-of-life score was assessed using the Minnesota Living with HF questionnaire (14). To ascertain biventricular pacing, a surface electrocardiogram was obtained at all visits. Exercise tolerance was evaluated using a 6-min walk test at all visits (15). Resting 2-dimensional echocardiography was performed at baseline and 6 months follow-up to assess LVEF. From the apical 2- and 4-chamber images, LVEF was determined using the biplane Simpson's rule (16).

After 6 months, patients were classified as responders, based on an improvement in NYHA functional class by ≥1 and/or an improvement by ≥25% in 6-min walking distance, or as non-responders based on lack of improvement.

Thereafter, follow-up at the outpatient clinic was scheduled at regular intervals. Events were classified as cardiac death (e.g., arrhythmic death, sudden cardiac death, death attributable to congestive HF, or myocardial infarction), non-cardiac death, and heart transplantation.

Statistical analysis. Continuous data are presented as mean ± SD; dichotomous data are presented as numbers and percentages. Differences in baseline characteristics and 6-month follow-up between independent patient groups are evaluated using unpaired Student *t* (continuous variables) and chi-square tests as well as a Mann-Whitney test (NYHA functional classification). Yates correction was used in tables with a total <100 or with any cell containing a value <10. Data within patient groups (to compare the effect of CRT) were compared by the use of paired Student *t* tests (continuous variables) and Wilcoxon signed-rank tests (NYHA functional classification). Event and survival curves were determined according to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test.

Univariable and multivariable Cox regression analyses were performed to determine a relation between potential risk factors at baseline, and the incidence of ICD therapy in primary prevention patients, secondary prevention patients, and both (primary end point); and death from any cause

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during long-term follow-up (secondary end point). We considered the following variables: age, gender, etiology, QRS duration, LVEF, medication, previous infarction, and comorbidity. Responding to CRT and the indication for ICD therapy were added in the analysis of incidence of ICD therapy in all patients. All variables entered the multivariable stage, irrespective of the results of the univariable analyses. Multivariable regression was then performed according to the principle of backward deletion. All variables with a p value of <0.25 remained in the final model. We report only adjusted hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs).

For all tests, a p value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics. A total of 195 consecutive patients with advanced HF underwent CRT-ICD implantation. The procedure was successful in all patients and, except for pocket hematoma in 9 and a pneumothorax in 1, no procedure-related complications were observed. One patient died 1 day after a "rescue" procedure due to refractory cardiogenic shock. Three patients were lost for follow-up (all primary prevention patients). Follow-up of the remaining 191 CRT-ICD patients (age 64 ± 11 years, 153 men) (Table 1) was 18 months (range 25 days to 2 years). Underlying etiology was ischemic in 107 patients (56%) and non-ischemic in 84 patients (44%); NYHA functional class before implant was 2.9 ± 0.5, QRS duration was 163 ± 30 ms, and LVEF was 21 ± 7%. According to the initial indication for ICD implantation, 120 patients (101 prophylactic, 14 patients with non-sustained VT on Holter monitoring without inducible VT, 5 patients with syncope without observed or inducible VT) were allocated to the primary prevention group (group 1); the secondary prevention group (group 2) contained 71 patients (11 patients with inducible VT, 38 patients with spontaneous VT, and 22 out-of-hospital cardiac arrest survivors).

Patients in the secondary prevention group were more likely to have an ischemic cardiomyopathy (70% vs. 48%, $p < 0.01$) and a previous myocardial infarction (62% vs. 32%, $p < 0.01$). Usage of amiodarone was significantly higher in the patients with prior ventricular arrhythmias. Among patients in the primary prevention group, amiodarone was initiated for the suppression of atrial fibrillation (n = 18, 15%), whereas among secondary prevention patients amiodarone (n = 39, 55%) was used for atrial arrhythmia suppression in 4, VT suppression in 27, and both in 8 patients.

Incidence and therapy of ventricular arrhythmias. During follow-up, the incidence of ventricular arrhythmias (as monitored by the device) was 24% in the primary prevention group and 39% in the secondary prevention group ($p < 0.05$) (Table 2). The first ventricular arrhythmia episode was terminated by ATP and/or shocks in 50 patients (88%). Ventricular arrhythmias (>10 beats) with a cycle length in the monitor zone received no therapy (12%). After the first episode of ventricular arrhythmias, the parameter settings of the ICD were adjusted.

As expected (despite a significantly higher usage of antiarrhythmic drugs), secondary prevention patients received more appropriate ICD therapy (n = 25, 35%, 95%

Table 1. Baseline Characteristics

Variables	Primary Prevention (n = 120)	Secondary Prevention (n = 71)	All Patients (n = 191)
Men	94 (78%)	59 (81%)	153 (79%)
Age (yrs)	64 ± 10	66 ± 11	64 ± 11
Follow-up (months)	19 ± 6	18 ± 7	18 ± 6
Etiology			
Ischemic	57 (48%)	50 (70%)*	107 (56%)
Non-ischemic	63 (52%)	21 (30%)*	84 (44%)
QRS duration (ms)	163 ± 30	164 ± 29	163 ± 30
Rhythm			
Sinus rhythm	87 (73%)	50 (70%)	138 (72%)
Paroxysmal atrial fibrillation	27 (22%)	15 (21%)	42 (22%)
Permanent atrial fibrillation	6 (5%)	6 (8%)	12 (6%)
Pacemaker rhythm	12 (10%)	9 (13%)	21 (11%)
LVEF (%)	22 ± 7	20 ± 7	21 ± 7
NYHA functional class	2.9 ± 0.5	3.0 ± 0.5	2.9 ± 0.5
CRT-ICD indication			
Prophylactic	101 (84%)	0 (0%)	101 (53%)
Non-sustained VT	14 (12%)	0 (0%)	14 (7%)
Syncope	5 (4%)	0 (0%)	5 (3%)
Inducible VT	0 (0%)	11 (15%)	11 (6%)
Spontaneous VT	0 (0%)	38 (54%)	38 (20%)
Spontaneous VF	0 (0%)	22 (31%)	22 (12%)
Cardiovascular history			
Previous infarction	38 (32%)	44 (62%)*	82 (43%)
Previous PCI	17 (14%)	16 (23%)	33 (17%)
Previous CABG	28 (23%)	13 (18%)†	41 (21%)
Previous valve surgery	10 (8%)	8 (11%)	18 (9%)
Previous device	16 (13%)	29 (41%)*	45 (24%)
Pacemaker	10 (8%)	8 (11%)	18 (9%)
ICD	2 (2%)	21 (30%)*	23 (12%)
CRT	4 (3%)	0 (0%)	4 (2%)
Comorbidity			
Diabetes mellitus	24 (20%)	13 (18%)	37 (19%)
Stroke/TIA	8 (7%)	15 (21%)*	23 (12%)
Peripheral vascular disease	11 (9%)	7 (10%)	18 (9%)
COPD	18 (15%)	7 (10%)	25 (13%)
Medication			
Antithrombotic therapy	107 (89%)	59 (83%)	166 (87%)
ACE inhibitor/ATII blocker	103 (86%)	58 (82%)	161 (84%)
Diuretic	98 (82%)	61 (86%)	159 (83%)
Spironolactone	54 (45%)	32 (45%)	86 (45%)
Beta-blocker (including sotalol)	72 (59%)	33 (46%)	105 (55%)
Statin	50 (42%)	33 (46%)	83 (43%)
Digoxin	30 (25%)	19 (27%)	49 (26%)
Amiodarone	18 (15%)	39 (55%)*	57 (30%)

*$p < 0.01$ compared with primary prevention group; †$p < 0.025$ compared with primary prevention group.

ACE = angiotensin-converting enzyme; ATII = angiotensin II receptor; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2. Cardiovascular Events

Variables	Primary Prevention (n = 120)	Secondary Prevention (n = 71)	All Patients (n = 191)
Deaths	4 (3%)	13 (18%)*	19 (9%)
Heart transplantation	1 (1%)	1 (1%)	2 (1%)
Ventricular arrhythmia (VT/VF)	29 (24%)	28 (39%)*	57 (30%)
Appropriate ICD therapy	25 (21%)	25 (35%)*	50 (26%)
Inappropriate shock	6 (5%)	8 (11%)	14 (7%)
Cycle length of first ventricular arrhythmia (ms)	313 ± 69	335 ± 13	324 ± 107
Time to first appropriate ICD therapy (months)	9 ± 6	8 ± 7	9 ± 7
Cutoff rate VT zone (beats/min)	164 ± 18	167 ± 19	165 ± 18

*$p < 0.01$ compared with primary prevention group.
Abbreviations as in Table 1.

CI 24 to 46%) than primary prevention patients (n = 25, 21%, 95% CI 14 to 28%, $p < 0.05$). The 1-year ICD therapy rate in the primary prevention group (although lower than the 27% event rate in the secondary prevention group, $p = 0.01$) was 15% (Fig. 1).

Of interest, the time between implant and first appropriate ICD therapy was similar in both groups (group 1: 9 ± 6 months; group 2: 8 ± 7 months, p = NS). Furthermore, the cycle length of the first ventricular arrhythmia triggering ICD therapy was the same in both groups (324 ± 107 ms), and the average cutoff rate of the VT detection zone was set at 165 ± 18 beats/min in both groups.

Predictors of ICD therapy. No differences were observed in baseline clinical parameters between patients who received appropriate ICD therapy and patients who did not receive therapy. No predictors of ICD therapy could be identified by multivariate analysis (including etiology, gender, age, QRS duration, LVEF, medication, previous infarction, and comorbidity) in primary prevention patients. In secondary prevention patients, however, age (<65 years, HR 0.249, 95% CI 0.066 to 0.941, $p < 0.05$) and amiodarone usage (HR 0.150, 95% CI 0.040 to 0.565, $p < 0.05$) were associated with a decreased risk of ICD therapy.

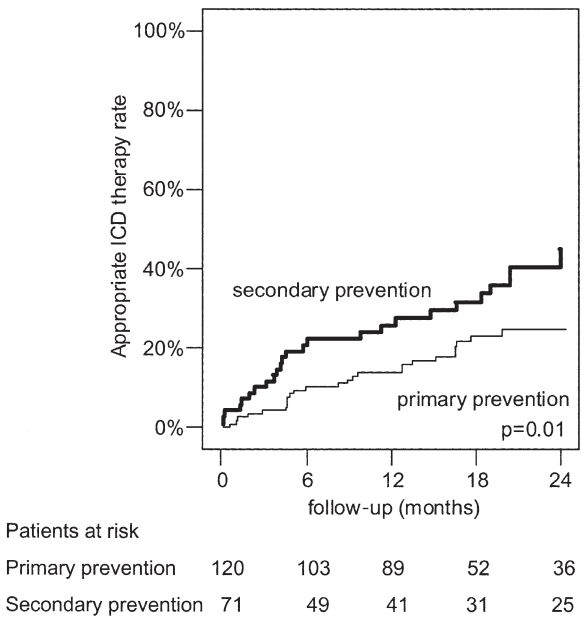

Figure 1. Appropriate implantable cardioverter-defibrillator (ICD) therapy rate in primary and secondary prevention patients.

Inappropriate therapy. Fourteen patients (7%) experienced inappropriate shocks (5% primary prevention group, 11% secondary prevention group, p = NS). The trigger for inappropriate therapy was atrial arrhythmia in 10 patients, sinus tachycardia in 2 patients, T-wave oversensing in 1 patient, and sensing of diaphragm potentials in 1 patient.

Clinical parameters. At baseline, no differences in NYHA functional class, LVEF, and QRS duration were observed between primary and secondary prevention patients. After CRT implantation, NYHA functional class improved ≥1 class in 145 patients (76%) and quality-of-life score changed from 40 ± 16 to 24 ± 19 ($p < 0.01$). In addition, the exercise capacity improved, as reflected by an increase in 6-min walking distance from 300 ± 137 m to 403 ± 144 m ($p < 0.01$) after 6 months of CRT. There were no significant differences in clinical outcome parameters between the 2 groups (Table 3).

Accordingly, primary and secondary prevention patients responded equally to CRT therapy (75% vs. 77%, p = NS).

However, patients with ATP/shocks had, in contrast with patients without ATP/shocks, a lower response rate to CRT (65% vs. 80%, $p < 0.025$) (Table 4). Vice versa, clinical response to CRT resulted in a 69% lower risk of

Table 3. Clinical Parameters in Primary and Secondary Prevention Patients

Variables	Primary Prevention (n = 120)	Secondary Prevention (n = 71)	All Patients (n = 191)
NYHA functional class			
Baseline	2.9 ± 0.5	3.0 ± 0.5	2.9 ± 0.5
Follow-up	1.9 ± 0.6*	2.0 ± 0.6*	1.9 ± 0.6*
Quality of life, questionnaire			
Baseline	40 ± 16	39 ± 17	40 ± 16
Follow-up	24 ± 21*	23 ± 16*	24 ± 19*
6-min hall walk test (m)			
Baseline	297 ± 145	305 ± 123	300 ± 137
Follow-up	401 ± 155*	407 ± 123*	403 ± 144*
Responder	90 (75%)	55 (77%)	145 (76%)

*$p < 0.01$ compared with baseline parameters.
NYHA = New York Heart Association.

Table 4. Clinical Parameters in Patients With and Without ICD Therapy

Variables	Patients With ICD Therapy (n = 50)	Patients Without ICD Therapy (n = 141)
NYHA functional class		
Baseline	3.0 ± 0.5	2.9 ± 0.5
Follow-up	2.1 ± 0.6*	1.9 ± 0.6*
Quality of life, questionnaire		
Baseline	41 ± 17	40 ± 16
Follow-up	28 ± 16*	23 ± 20*
6-min hall walk test (m)		
Baseline	296 ± 124	301 ± 142
Follow-up	385 ± 146*	409 ± 143*
Responder	32 (65%)	113 (80%)†

*$p < 0.01$ compared with baseline parameters; †$p < 0.025$ compared with patients with ICD therapy.
Abbreviations as in Table 1.

receiving ICD therapy in both groups (HR 0.308, 95% CI 0.099 to 0.962, $p < 0.05$).

Long-term follow-up. Seventeen (9%, group 1: 4 [3%]; group 2: 13 [18%]) patients died within the 2-year follow-up period. Most deaths were due to end-stage HF; 1 patient died after myocardial infarction. No arrhythmic deaths were observed. Two patients underwent heart transplantation.

Despite identical baseline functional status, secondary prevention patients accounted for more deaths than primary prevention patients (18% vs. 3%, $p < 0.05$) (Table 2). The 1-year survival was 91% in the secondary prevention group and 99% in the primary prevention group with a 2-year survival of, respectively, 96% and 79% (Fig. 2).

Multivariate analysis revealed advanced age and amiodarone usage as independent predictors of death. Previous ventricular arrhythmias, etiology, and response to CRT had, however, no influence on the relative risk of death. Importantly, ICD therapy was not correlated with lives saved (HR 1.185, 95% CI 0.305 to 4.598, p = NS).

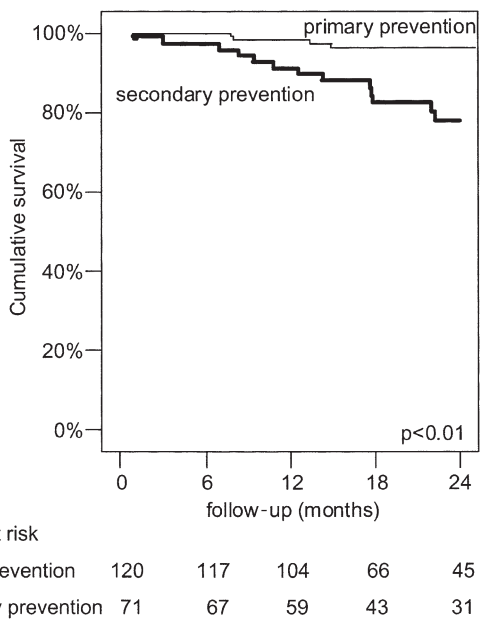

Figure 2. Survival curve for primary and secondary prevention patients.

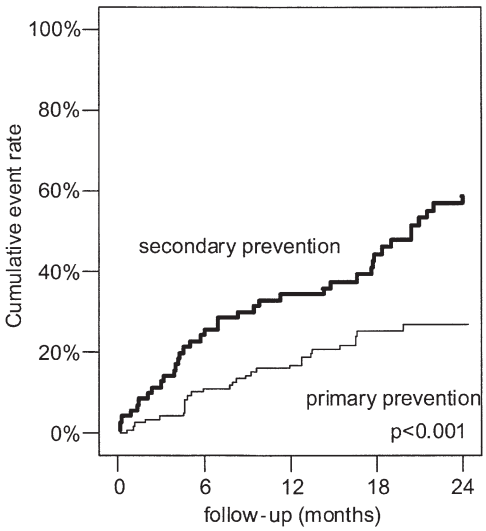

Figure 3. Cardiac event curve for primary and secondary prevention patients.

The cumulative cardiac event rate including appropriate therapy (ATP/shock), death, and heart transplantation is shown in Figure 3. The 2 curves (primary and secondary prevention patients) diverge immediately after implant and continue their paths, resulting in a 1-year event rate of 17% in patients without arrhythmias and of 34% in patients with arrhythmias.

DISCUSSION

The main findings of this study were: 1) secondary prevention patients experienced more appropriate ICD therapy; however, 21% of the primary prevention patients received appropriate ICD therapy; 2) no predictors of ICD therapy in primary prevention patients could be identified; 3) patients with and without previous ventricular arrhythmias had a similar clinical benefit from CRT, although long-term follow-up showed a higher mortality rate in secondary prevention patients; and 4) clinical responders to CRT showed a lower number of ICD therapies compared with non-responders.

ICD therapy. Fifty patients (26%) experienced ventricular arrhythmias resulting in appropriate ICD therapy (ATP and/or shock) within 2 years after implant. As expected, and despite the higher use of amiodarone in the secondary prevention group, secondary prevention patients received significantly more ICD therapy than primary prevention patients (35% vs. 21%). However, the results obtained in the primary prevention group are in line with the results of the MADIT II (Multicenter Automatic Defibrillator Implantation) study (26% ICD therapy in ischemic cardiomyopathy patients, LVEF <30%) (13,17). Also, the SCD-HeFT study (LVEF <35%, ischemic and non-ischemic heart disease patients) reported an incidence of 21% ICD therapy,

though the follow-up period was longer in the SCD-HeFT study (10). In a retrospective review of 978 CRT-ICD patients of the MIRACLE-ICD (Multicenter InSync Implantable Cardioversion Defibrillation Randomized Clinical Evaluation) trial, it was reported that 28% of the secondary prevention patients experienced an appropriate shock at 12 months' follow-up, compared with only 14% of the primary prevention patients (18). Reported incidences of appropriate ICD therapy for secondary prevention patients vary from 53% (2-year follow-up) to 82% (10-year follow-up) (19–22). In our study, 35% of the secondary prevention patients received ICD therapy within 2 years of follow-up. Furthermore, in line with previous studies, time to first appropriate therapy was similar for both primary and secondary prevention patients (9 ± 7 months) (20,23).

Wilkoff et al. (18) reported that the cycle length of ventricular arrhythmias in primary prevention patients is shorter than the cycle length of ventricular arrhythmias in secondary prevention patients (303 ± 54 ms vs. 366 ± 71 ms, $p < 0.0001$). In part, this difference was explained by the rate-lowering effect of amiodarone, used by 44% of the secondary prevention patients and 23% of the primary prevention patients. In contrast, we found no differences in arrhythmia cycle length between the 2 groups. Notably, our study contained 22 survivors of VF, who tended to experience arrhythmias at a faster rate than patients initially treated because of sustained VT.

In this study, 23 patients with an ICD (2 primary prevention patients and 21 secondary prevention patients) received an upgrade to a CRT-ICD device. The potential beneficial effect of CRT on ventricular arrhythmias in patients with HF is incompletely understood. Some small studies reported a decrease of the number of ventricular arrhythmias after CRT, possibly due to LV reverse remodelling (24–27); however, others reported the opposite (28,29). A recently published meta-analysis of large randomized CRT trials found no statistically significant effect of CRT on VT/VF occurrence compared with ICD therapy only (30). Due to the relatively small number of patients, we were not able to detect a positive effect on VT/VF occurrence of CRT in the group of patients upgraded from ICD only to CRT-ICD.

As ICD therapy is costly and only 21% of the primary prevention patients received appropriate therapy, we tried to identify predictors of VT/VF in this group. However, we could not identify predictors of VT/VF in primary prevention patients eligible for CRT.

Response to CRT. The baseline characteristics of both groups were (with the exception of the higher number of ischemic heart disease patients in the secondary prevention group and higher amiodarone usage in this group) more or less identical. Furthermore, the efficacy of CRT, as reflected by the improvement of functional status, was similar in both groups, which is in line with the results of larger randomized trials (3,4,6,7,11).

As reported by others, not all patients (46 patients, 24%) responded to CRT. This relatively high number reflected the inability to predict a positive outcome by applying the current inclusion criteria and warrants a further refinement of these criteria (3,31,32). Of interest, response to CRT was associated with a lower risk of receiving ICD therapy.

Mortality. Two-year mortality was 9%. No arrhythmic deaths were observed, and most deaths were HF related. Large randomized HF trials in patients without ventricular arrhythmias reported 2-year mortality rates between 12% and 30%, which is much higher compared with the 4 primary prevention patients who died in this study (2-year mortality rate 4%, Fig. 2) (8,10,11,13). Notably, sudden cardiac death accounted for 35% of all deaths in the CARE-HF study (8).

In contrast, the 18% mortality rate observed in secondary prevention patients was comparable to the mortality rate reported by some secondary sudden cardiac death prevention trials (9). Secondary prevention patients were more likely to have ischemic heart disease, more previous myocardial infarctions, more ventricular arrhythmias, and a higher amiodarone usage: in other words, comprise a sicker patient group. As expected, advanced age (>65 years) was associated with a higher mortality rate. Furthermore, amiodarone usage was also found to be an independent predictor of death. This is in line with a recent study by Kies et al. (33), who evaluated 300 sudden cardiac death survivors with an ischemic cardiomyopathy. They also reported that amiodarone was associated with a higher mortality.

Study limitations. This was a non-randomized observational study performed to evaluate outcome differences between different ICD indication groups, which, actually, reflect daily clinical practice. A control group would have underlined our results; however, all patients had an ejection fraction below 35% and therefore an indication for an ICD insertion, as well as an indication for CRT. The primary and secondary prevention groups were not entirely comparable; the secondary prevention group accounted for many more ischemic patients. However, etiology was not identified as an independent predictor for ICD therapy or death.

Power calculation was not performed in this prospective study, because the incidence of ICD therapy in patients with and without prior ventricular arrhythmias was unknown at the start of the study. The sample size of 191 patients may be too small to identify predictors of VT/VF, and explains its inability to predict them. Also, assumption of the clinical efficacy of ICD therapies is needed, because the number of ICD therapies does not correlate with the number of lives saved from SCD. Larger studies are needed to further evaluate these issues.

Conclusions. Despite a higher incidence of VT/VF episodes in secondary prevention patients, 21% of the primary prevention patients did receive appropriate ICD therapy during follow-up, and no predictors could be identified before implant. Furthermore, CRT is effective in HF patients with and without prior ventricular arrhythmias.

Interestingly, patients responding to CRT received less ATP or shocks.

These data suggest that a combined CRT-ICD device should be implanted in all patients eligible for CRT. However, the data also suggest that specificity of the selection criteria for ICD therapy is low, and efforts should be made to increase the number of patients who will truly benefit from combined CRT-ICD therapy.

Reprint requests and correspondence: Dr. Martin J. Schalij, Department of Cardiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, the Netherlands. E-mail: M.J.Schalij@LUMC.nl.

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