

# Predictors for early mortality and arrhythmic events in patients with cardiac resynchronization therapy with defibrillator: A two center cohort study

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## Abstract

**Background:** Guidelines of heart failure therapy include cardiac resynchronization as standard of care in patients with severely depressed left ventricular function and wide QRS complex. It has been shown that patients benefit regarding mortality and morbidity. However, early mortality precludes long-term benefits from the device. The aim of the study was to identify predictors for early occurrence of both death and first-ever implantable cardioverter-defibrillator (ICD) therapy using a large combined database of patients with cardiac resynchronization therapy with defibrillator (CRT-D).

**Methods:** From two registries (tertiary care centers) 904 patients were identified, no single patient was excluded. Early death was defined as death occurring within the 3 years after implantation whereas early ICD therapy as such occurring within the first year. 33 baseline parameters were compared using uni- and multivariate analysis with the Cox model and binary logistic regression.

**Results:** The population was predominantly male (77%), with mean age of  $63 \pm 11$  years and primary prevention indication in 80%. Mean follow-up was  $55 \pm 38$  months. 256 (28%) patients had ICD therapies whereof the first-ever event occurred early in 52%. 270 (30%) patients died after  $41 \pm 31$  months, mostly from advancing heart failure (41%), 141 (52%) patients of them early. Independent predictors for early ICD therapy were secondary prevention and renal failure. Independent predictors for early mortality were a history of percutaneous coronary intervention and of peripheral vascular disease.

**Conclusions:** Predictors for early mortality after CRT-D implantation were a history of percutaneous coronary intervention and peripheral vascular disease, present in only a minority of patients, thus limiting their use in clinical practice. (Cardiol J 2019; 26, 6: 711–716)

**Key words:** cardiac resynchronization therapy, implantable cardioverter-defibrillator, mortality, predictive model, decision making

## Introduction

Implantation of a cardiac resynchronization therapy (CRT) device is standard of care in the therapy of heart failure patients with severely depressed left ventricular function and a wide QRS complex. Several randomized controlled trials have shown remarkable benefits of CRT regarding mortality and morbidity in combination with

an implantable cardioverter-defibrillator (ICD) but also with a stand-alone pacemaker [1, 2]. Many patients present with left ventricular ejection fraction (LVEF) below 35%, and thus are implanted with a CRT defibrillator (CRT-D). However, no strong evidence suggests that CRT-D must be used in all patients that are CRT candidates [3]. A relevant number of patients have severe comorbidities and die early after implant. Therefore, they might not

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be in need of the ICD component of a CRT-D [4, 5]. Identification of such patients is considered important, as death as the competing event obviously precludes potential long-term benefit from the ICD component of CRT. Data regarding first-ever ICD therapy are conflicting; studies have shown both linear and asymptotic event curves [6–8]. The aim of this study was to determine independent predictors for early occurrence of both death and first-ever ICD therapy. If meaningful and/or highly prevalent predictors were identified, they could help in decision making for CRT-D or for CRT-pacemaker (CRT-P).

## Methods

The study population consisted of all consecutive patients in whom a CRT-D was implanted at the Erasmus Medical Center, Rotterdam, the Netherlands or at the University of Basel Hospital, Switzerland. At the sites, patients are entered into separate registries that were started in Rotterdam in November 1999 ( $n = 608$  patients) and in Basel in February 2000 ( $n = 296$  patients). Last access to the database was July 2015 for Rotterdam patients and May 2015 for Basel patients. Data merging was performed in August 2015. No patients were excluded, leading to a total amount of 904 patients.

Deaths were classified as being due to progressive heart failure, clearly non-cardiac causes, sudden (i.e. a sudden death without post mortem analysis of the CRT-D and/or necropsy) or arrhythmic (i.e. the device could be interrogated showing either ventricular fibrillation that could not have been terminated by all shocks or sinus rhythm after successful shocks with subsequent electromechanical dissociation).

Patient and device characteristics are recorded prospectively at baseline, including 33 parameters such as demographic and cardiovascular items, comorbidities, drugs and laboratory values. Missing values of LVEF of 66 patients from Rotterdam were imputed as well as 5 missing values of blood urea nitrogen levels, and 2 values of QRS width and sodium, respectively, using the median of each parameter [9]. Renal failure was defined as glomerular filtration rate (GFR)  $< 60$  mL/min/1.73 m<sup>2</sup>. Appropriate ICD therapy are considered in the ventricular tachycardia (VT) zone of the ICD (tachycardia of 180–220/min, primarily terminated by antitachycardia pacing [ATP] or cardioversion shock if ATP failed) and in the ventricular fibrillation (VF) zone (tachycardias  $> 220$ /min terminated by ATP

during charging or by cardioversion shock). True ventricular fibrillation terminated by defibrillation was studied separately. In cases where ATP accelerated the VT into the VF zone, the initial VT was considered as the event of interest. The first-ever ICD therapy was defined as early when occurring within 12 months after implantation (median time of first-ever ICD therapy). Death was defined as early when occurring within 3 years after implantation (median time of death). All 33 baseline parameters were compared in univariate analysis for both events.

## Statistical analysis

Continuous variables are presented as mean  $\pm$  standard deviation or median with interquartile range and categorical variables as numbers and percentages. To determine the prognostic impact of significant variables, univariate Cox regression and binary logistic regression were used to compute hazard ratios (respectively odds ratios [ORs]) and 95% confidence intervals (CIs). All variables predicting death or ICD therapies significantly with a  $p$  value of  $\leq 0.1$  in the univariate model were entered in a multivariate model using the forward stepwise method. Statistical analyses were performed with the use of IBM SPSS Statistics for Windows, version 23.0 (SPSS Inc. Chicago, IL).

The study is a retrospective merged analysis of data collected prospectively in both centers.

## Results

### Baseline characteristics and follow-up

A merged population of 904 patients was predominantly male (77%), had a mean age of  $63 \pm 11$  years at implant and a primary prevention indication in 80%. Mean follow-up was  $55 \pm 38$  months. Table 1 depicts all relevant baseline characteristics in detail. Figure 1 shows a flow chart of patients included in the study, mortality rate and mode of death, the arrhythmias treated by the ICD, and their separation into early or non-early events.

### ICD therapies

During follow-up, 256 (28%) patients had ICD therapies. The first-ever event occurred early in 134 (52%) patients. In 2/3 ICD, therapy was delivered in the VT zone (82% of them occurring early), in 1/3, in the VF zone of the ICD (77% of them occurring early). Independent predictors for early ICD therapy were secondary prevention (OR 3.21, 1.84–5.56, 0.01) and renal failure (OR 2.08, 1.24–3.50, 0.01). More detailed data is presented in Tables 2 and 3.

**Table 1.** Baseline characteristics of the 904 patients.

Male gender	700 (77%)
Age at implant [years]	63 ± 11
Weight [kg]	82 ± 16
Body mass index	27 ± 5
Systolic BP [mmHg]	112 ± 19
Ejection fraction [%]	25 ± 7
QRS width [ms]	163 ± 29
Primary prevention	720 (80%)
Sinus rhythm	793 (88%)
NYHA I class	8 (1%)
NYHA II class	297 (33%)
NYHA III class	571 (63%)
Ambulatory NYHA IV class	28 (3%)
Clearance [mL/min/1.73 m <sup>2</sup> ]	64 ± 25
Renal failure (GFR < 60 mL/min/1.73 m <sup>2</sup> )	434 (48%)
Ischemic cardiomyopathy	451 (50%)
Myocardial infarction	371 (41%)
PCI	218 (24%)
CABG	191 (21%)
Diabetes mellitus	224 (25%)
Stroke	112 (12%)
COPD	107 (12%)
Cancer	70 (8%)
PVD	62 (7%)
Drug therapy:	
Diuretics	758 (84%)
ACE-inhibitors	751 (83%)
Beta-blockers	736 (81%)
Statins	508 (56%)
Aldosterone antagonists	416 (46%)
Angiotensin receptor blockers	216 (24%)
Amiodarone	202 (22%)
Digoxin	189 (21%)
Allopurinol	71 (8%)
Sodium [mmol/L]	139 ± 4
Hemoglobin [g/L]	134 ± 18
Blood urea nitrogen [mmol/L]	10 ± 6

ACE — angiotensin converting enzyme; BP — blood pressure; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; GFR — glomerular filtration rate; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; PVD — peripheral vascular disease

Independent predictors for VT as compared to fast VT/VF were beta-blocker therapy (OR 1.77, 1.09–2.86, 0.02) and increasing hemoglobin level (hazard ratio per 1 g/L 1.02, 1.01–1.04, 0.01).

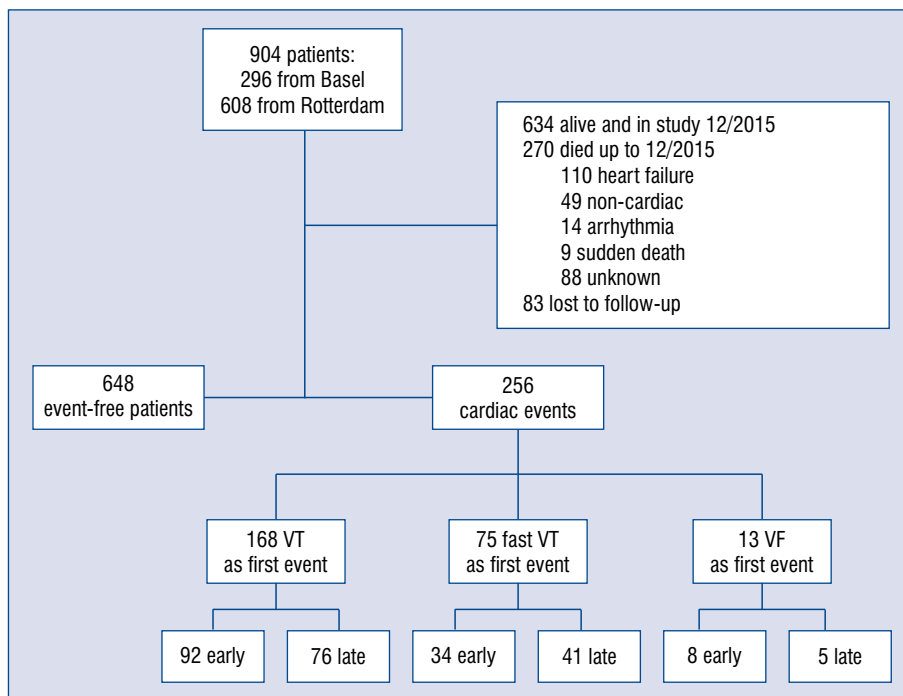
## Mortality

Overall, 270 (30%) patients died after a mean  $41 \pm 31$  months, mostly from advancing heart failure (41%) or non-cardiac causes (18%). Of note, the cause of death (not the time of death) was not recorded in the dataset in 33%. 141 (52%) patients had died within the first 3 years and thus early. Independent predictors for early mortality were a history of percutaneous coronary intervention (PCI) (OR 2.01, 1.10–3.66, 0.02) and peripheral vascular disease (PVD) (OR 2.91, 1.08–7.87, 0.04). However, only 24% of patients had a history of PCI and 7% of PVD. A more detailed overview is shown in Table 4.

## Discussion

During a mean follow-up of more than 5.5 years, only 28% of these CRT-D patients had appropriate ICD therapies. The first-ever event occurred early in 52%. A third of them were delivered for potentially life-threatening arrhythmias. This rate is slightly lower than the mortality of these severely sick patients (50% renal failure, 66% in the New York Heart Association [NYHA] class III or ambulatory class IV). With the inclusion of 33 parameters to study early ICD therapy and early mortality, it was determined that secondary prevention and renal failure were predictors for early ICD therapy and history of PCI and PVD for early mortality.

It would be both scientifically intriguing and clinically helpful to identify those patients who either die early after ICD implantation (and in whom CRT-D implantation can be questioned and CRT-P offered) or those who never experience ICD therapies. It is thus not surprising that several studies have been undertaken with the focus of early mortality [4, 6, 10, 11]. In the present study only history of PCI and PVD were identified as predictors for early mortality, i.e. at 3 years. However, the clinical application of them has to be questioned, as they were present in only 24% and 7% of patients, respectively. In addition, a sub-analysis from MADIT-CRT showed that a history of PCI, independent of frequency or timing before enrolment, did not influence mortality [12]. Finally, there is no intuitive explanation for these two identified predictors and, due to the low number of patients with these comorbidities, a type I error especially for PVD cannot be excluded. In summary, this study failed to fulfil the particular aim of predicting early mortality in a clinically applicable way.



**Figure 1.** Flow chart of patients and cardiac events; VT — ventricular tachycardia (> 180/min); fast VT — fast ventricular tachycardia (> 220/min); VF — true ventricular fibrillation.

**Table 2.** Univariable and multivariable analysis for occurrence of first-ever implantable cardioverter-defibrillator therapy without temporal discrimination (only significant parameters are shown, hazard ratio < 1 = no cardiac event, hazard ratio > 1 = cardiac event).

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Secondary prevention	1.596	1.232–2.068	0.000	1.534	1.183–1.990	0.001
Renal failure	1.468	1.142–1.888	0.003	1.408	1.093–1.814	0.008
Amiodarone therapy	1.423	1.075–1.883	0.014	–		
Clearance [mL/min/1.73 m <sup>2</sup> ]	0.993	0.987–0.999	0.014	–		
Age at implant [year]	1.015	1.005–1.026	0.004	–		
Blood urea nitrogen [mmol/L]	1.022	0.998–1.046	0.074	–		

CI — confidence interval; HR — hazard ratio

In CRT-D patients, no similar data are available to date. In a large ICD only cohort study with a validation cohort (total patient number 2700, 75% primary prevention) [10], four factors predicted mortality at 1 year. They were PVD, age > 70 years, LVEF < 20% and creatinine > 176 mmol/L. Patients with only one factor had a mortality of 4% as compared to 18% in those with four factors. Results were confirmed in a population of 800 patients (100% primary prevention, 28% CRT-D) [4]. Age (here: > 75 years), impaired renal function (here:

GFR < 30 mL/min/1.73 m<sup>2</sup>), QRS width > 120 ms, and atrial fibrillation were the four predictors. Mortality at 1 year was 2.5% in patients with 0 or 1 risk factors, but 46% in those with all four factors present. However, both papers do not discuss the fact that only 2% of patients were labelled as very high-risk patients, which renders the usefulness of these impressive results less applicable in daily life.

In a study of 225 octogenarians, LVEF < 20% and lack of beta-blocker therapy were the only two

**Table 3.** Uni- and multivariable analyses for occurrence of first-ever implantable cardioverter-defibrillator therapy with discrimination between early and late events (only significant parameters are shown, odds ratio < 1 = early [ $\leq$  12 months], odds ratio > 1 = late [ $>$  12 months]).

	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Secondary prevention	0.302	0.175–0.521	0.000	0.312	0.180–0.543	0.000
Renal failure	0.457	0.277–0.754	0.002	0.480	0.286–0.807	0.006
Amiodarone therapy	0.623	0.355–1.092	0.098			–
ARB therapy	1.671	0.935–2.987	0.083			–
Age at implant [year]	0.969	0.948–0.990	0.005			–
Weight [kg]	1.018	1.001–1.034	0.036			–
Blood urea nitrogen [mmol/L]	0.951	0.906–0.998	0.040		–	
Clearance [mL/min/1.73 m <sup>2</sup> ]	1.016	1.005–1.027	0.006		–	
Hemoglobin [g/L]	1.015	1.002–1.029	0.029			–

ARB — angiotensin receptor blocker; CI — confidence interval; OR — odds ratio

**Table 4.** Uni- and multivariable analyses for occurrence of early death (only significant parameters are shown, odds ratio < 1 = early [ $\leq$  36 months], odds ratio > 1 = late [ $>$  36 months]).

	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Ischemic cardiomyopathy	0.651	0.396–1.071	0.091	–		
PCI	0.556	0.318–0.973	0.040	0.498	0.273–0.908	0.023
Diabetes mellitus	0.639	0.376–1.086	0.098	–		
PVD	0.313	0.121–0.811	0.017	0.344	0.127–0.930	0.035
Renal failure	0.440	0.265–0.729	0.001	–		
Digoxin therapy	0.600	0.354–1.018	0.058	–		
Weight [kg]	1.019	1.003–1.035	0.019	–		
Body mass index [Unit]	1.051	1.000–1.104	0.050	–		
Systolic BP [mmHg]	1.012	0.999–1.024	0.073	1.015	1.002–1.029	0.025
Blood urea nitrogen [mmol/L]	0.963	0.926–1.000	0.050	–		
Clearance [mL/min/1.73 m <sup>2</sup> ]	1.018	1.007–1.029	0.001	1.020	1.009–1.031	0.001
Hemoglobin [g/L]	1.013	0.999–1.026	0.060	–		

BP — blood pressure; CI — confidence interval; OR — odds ratio; PCI — percutaneous coronary intervention; PVD — peripheral vascular disease

predictors of mortality at 1 year. Mortality of patients with LVEF < 20% was threefold compared to those with LVEF > 20%, but the patient number at risk are not mentioned, thus severely limiting this statement. Finally, the Italian IRIDE registry [6] reported their results on 600 patients with primary prevention (43% CRT-D). They showed a linear increase of mortality to 24% at 4 years, which is similar to the present results. This is surprising, given the much higher disease burden in the current study (48% renal failure and 71% NYHA class

III/IV vs. 11% and 38%, respectively). In addition, even though ICD programming is comparable, the rate of ICD therapies was as high as 50% after 5 years, as opposed to 28% in the study herein.

Other factors are also not especially analyzed in this paper, as e.g. metabolic syndrome with or without obesity, were not shown to influence mortality [13].

To identify predictors of ICD therapy, early or rather late after implantation, is less useful in daily life. This is because a) there are data [7] showing that a substantial proportion of patients have

their first ICD therapy after 5 years and b) especially in secondary prevention guidelines regarding continuation of ICD treatment even in patients without ICD therapy for many years are clear-cut. Nevertheless, this issue has been investigated herein. In the present CRT-D population, only two predictors could be identified (after analysing 33 parameters) for early ICD therapy, secondary prevention (which is commonly known) and renal failure. A Dutch cohort study [8] did not find a predictor using eight parameters. Identifying predictors that somehow “protect” patients from early or late ICD therapy seems alluring at first glance, as one could argue that such a patient might not be in need of the ICD part of CRT. Further studies especially in patients with dilated cardiomyopathy are needed that include parameters not used in the present dataset such as a true left bundle branch block as compared to other forms of QRS widening or late gadolinium enhancement as seen on magnetic resonance imaging.

### Limitations of the study

This study has all the limitations of a retrospective database study. There was no “control group” with patients with only CRT-P, who might have had other predictors for early death other than CRT-D patients. Some data had to be imputed. Finally, about 10% were lost to follow-up, and in about the same percentage, the mode of death was unknown. This does, however, not influence prediction of early mortality, as the analysis was performed regarding all-cause mortality.

### Conclusions

Predictors for early mortality after CRT-D implantation were a history of PCI and PVD, however present in only a minority of patients. A survey of the available literature suggests that it is difficult to predict early mortality, albeit this would impact on those patients with a high chance of dying and have no benefit from the ICD part of CRT.

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