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Persistent improvement of ejection fraction in patients with a cardiac resynchronisation therapy defibrillator correlates with fewer appropriate ICD interventions and lower mortality

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Summary

QUESTION UNDER STUDY: Cardiac resynchronisation therapy with defibrillator back-up (CRT-D) is a well-established treatment option for selected heart failure patients. Left ventricular ejection fraction (LVEF), an important risk determinant of life-threatening arrhythmias, can substantially ameliorate with CRT. Our hypothesis was that patients with LVEF improvement to >40% have a lower arrhythmic risk and fewer appropriate defibrillator therapies beyond year one.

METHODS: In this retrospective analysis, all 175 patients with CRT-D implanted from February 2000 to June 2011 and follow-up of >2 years were identified. Every available echocardiography recording was collected. LVEF measurements were grouped to baseline and yearly intervals (±6 months). All appropriate defibrillator therapies were considered events.

RESULTS: Age at implant was 65 ± 10 years, 86% were male, and 45% patients had ischemic cardiomyopathy. Follow-up was 5.5 ± 2.6 years. LVEF at implant was 25 ± 6%, increased to 34 ± 12% after one year and remained stable thereafter. 39% (69) of patients experienced a sustained increase of LVEF to ≥40%, 14% of them had tachyarrhythmic events (versus 42.5% in those without such increase). Independent predictors for increase were higher baseline LVEF (HR 1.08 (95%-CI 1.04–1.28) per 1% increase) and lack of amiodarone (HR 0.37, 95%-CI 0.16–0.84). With cut-off values of >40%, >45% and >50%, the study hypothesis was refuted in 7%, 2.5% and 5%, respectively. Cumulative 5-year survival was 95% in improvers versus 73% in non-improvers (p <0.001).

CONCLUSION: After CRT-D implantation, mean LVEF increased to >40% in 1/3 of patients. These patients experienced significantly fewer arrhythmias during long-term follow-up when compared to patients with persisting LVEF <40%.

Key words: *cardiac resynchronisation therapy (CRT); cardiac resynchronisation therapy pacemaker (CRT-P); cardiac resynchronisation therapy plus defibrillator (CRT-D); implantable cardioverter defibrillator (ICD); long-term follow-up; left ventricular ejection fraction (LVEF)*

Introduction

Cardiac resynchronisation therapy (CRT) is a class I, level A indication for those patients in sinus rhythm under optimal medical therapy who present with New York Heart Association (NYHA) classes II, III or ambulatory IV, a left ventricular ejection fraction (LVEF) ≤35%, left bundle-branch block (LBBB) morphology with a QRS duration of ≥150 ms (≥120 ms: class I, level B) [1]. Significant reductions in morbidity and mortality have been shown in randomised controlled trials [2, 3]. Improvements in structure or function of the left ventricle usually occur early after CRT implantation and consist of one or more of the following items: improvement in LVEF [3–12]; reductions of left ventricular volume [4, 7], end-systolic volume index [3] and mitral regurgitation [3, 7]. Functional improvements for patients can encompass a reduction in NYHA class [3, 4] as well as an improvement in quality of life [3] or in the 6-minute walking test [13]. Effects are summarised under the term of "reverse remodelling". CRT can be combined with a defibrillator back-up (CRT-D) or used as a stand-alone therapy (CRT-P). Since most patients meet the indication criteria for a primary prevention implantable cardioverter defibrillator (ICD) at the time of implant, CRT-D is usually implanted [14]. An inverse correlation between an increase in LVEF and a reduction of appropriate ICD therapies [15–19] or, more specifically, life-threatening arrhythmias has been described [17, 20], albeit with a limited follow-up period.

Therefore, the aim of this study was to correlate improvements in LVEF with the incidence of appropriate ICD therapies and death during long-term follow-up. Our hypothesis was that patients in whom LVEF raises to >40% have fewer appropriate ICD-therapies beyond year one (when reverse remodelling, if ever, has occurred).

Methods

All ICDs that are implanted at the University of Basel Hospital are included in a prospective registry. At implant, several cardiological parameters, comorbidities and laboratory values are collected. The registry is continuously updated for appropriate ICD therapies and deaths. All 265 CRT-D patients in whom a device was implanted between February 2000 and March 2014 were identified. Ninety (34%) patients with a CRT-D implantation not according to current guidelines (6 patients with LVEF >35% and 12 with QRS width <120 ms) or a follow-up of less than 2 years were excluded (see fig. 1). File closure was on the 31 May 2014.

All available reports from device follow-up visits and echocardiographic examinations were retrieved. Device follow-ups were performed after 1, 3 and 6 months and then every 6 months. No structured protocol was defined for follow-up echocardiography, but studies once a year or at clinical necessity and the application of the modified Simpson's method in a biplane mode [21] to determine LVEF were strongly encouraged. Values of LVEF were pooled into yearly groups of ±6 months. According to guidelines, the only determiner for CRT-D (compared to CRT-P) is LVEF ≤35%, and therefore we strictly focused our study on this parameter. [22] Other validated parameters indicating reverse remodelling, such as left ventricular end-systolic volume [10, 23] or regression of left ventricular mass [7], were not considered. We would like to stress that this study is hence not on reverse remodelling and does also not report on clinical benefit to patients. Sustained LVEF improvement was defined as an increase of LVEF to ≥40% determined at the last available echocardiography. To facilitate reading, such patients are named "improvers" as opposed to "nonimprovers". Appropriate interventions of the ICD could be either in the ventricular tachycardia (VT) zone (when faster than 180/min and terminated by antitachycardia pacing [ATP]) or in the ventricular fibrillation (VF) zone of the device (when faster than 230/min and terminated by shock).

Continuous variables are presented as mean (± SD) and categorical variables as numbers and percentages. Continuous variables were compared with the use of the student's t-test and categorical variables with the use of the chi-square test. All significant variables in the univariable model were then tested in a multivariable model using the forward stepwise method. Hypothesis testing was two-tailed, and p-values of <0.05 were considered to indicate statistical significance. Hazard ratios (HRs) were determined with Cox regression analysis. All statistical analyses were performed with the use of IBM SPSS Statistics for Windows, version 22.0 (SPSS Inc. Chicago, IL).

The study conforms to the principles outlined in the Declaration of Helsinki [24] and was approved by the ethical review committee of Basel/Switzerland (EKBB 229/2012).

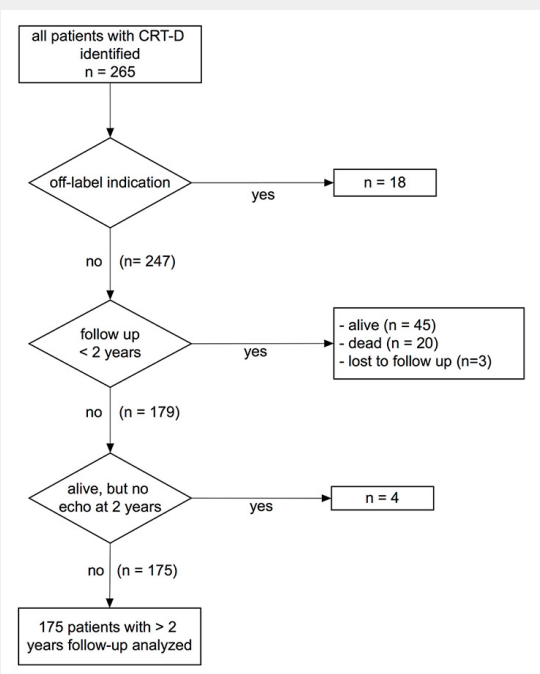

Figure 1

Flow-chart of all patients with a cardiac resynchronisation therapy with defibrillator back-up device (CRT-D) implanted at our hospital.

Results

The study population of 175 patients was predominantly male (85%) with a mean age of 65 ± 10 years. Ischaemic cardiomyopathy was present in 44%, and the majority was in NYHA class III (68%). Mean follow-up was 5.5 ± 2.6 years. Baseline characteristics are shown in table 1. Amiodarone was prescribed to 22/141 patients with primary and to 17/34 patients with secondary prevention ICD indication (16%/50%), p value <0.0001.

Echocardiographic long-term improvement to an LVEF of >40% was seen in 69 patients (39%). Annual box-plots of patients with and without improvement are shown in figures 2 and 3. Mean increase from baseline LVEF to last follow-up was 27 to 48% in improvers and 24 to 28% in nonimprovers. In both groups, the increase was significant (p value <0.005) at the time point 1 year and remained stable thereafter. The only two independent predictors for improvement to ≥40% were higher baseline LVEF (HR 1.08, 95% confidence interval [CI] 1.04–1.28, per 1% in-

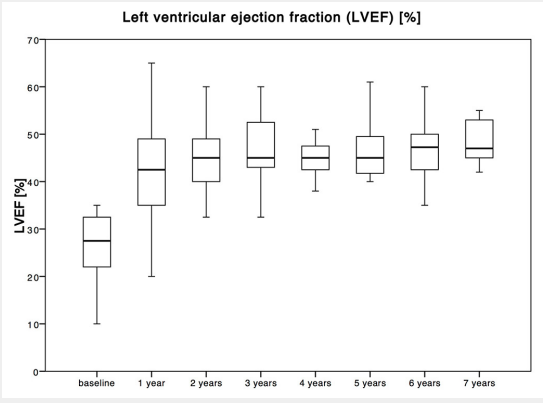

Figure 2

Changes in ejection fraction during long-term follow-up in patients with improvement to >40% (boxes indicate the interquartile range, whiskers 1.5-fold the length of the box).

crease in LVEF) and lack of amiodarone therapy (HR 0.37, 95% CI 0.16—0.84).

Up to file closure, 40 study patients (23%) had died after a mean of 4.2 ± 1.9 years. A Kaplan-Meier curve is shown in figure 4. Cumulative 5-year survival was 95% in improvers versus 73% in nonimprovers (p <0.001). In multivariate analysis, five independent predictors for mortality were established. These were lower baseline LVEF (HR 0.92, 95% CI 0.85–0.98, per 1% decrease in LVEF), history of cancer (HR 2.97, 95% CI 1.03–8.59), renal failure (HR 2.95 95% CI 1.31–6.65), treatment with digitalis (HR 4.19, 95% CI 1.30–13.48) and lack of β-blocker therapy (HR 4.76, 95% CI 1.68–13.51).

Improvers were less likely to experience any appropriate ICD therapy (14.5% [10/69] vs 42.5% [45/106], p = 0.0001). The overall rate was 31%. ICD "use" was mainly driven by treatment of tachycardias in the VT zone (10.1% [7/69] vs 29.2% [31/106], p = 0.003) compared with those in the VF zone >230 bpm (4.3% [3/69] vs 13.2% [14/106], p = 0.07). Details are shown in table 2. The rate of inappropriate therapies was similar between groups (2.9% in improvers, 5.7% in nonimprovers, p = 0.48).

During follow-up, ten improvers (15%) had a tachyarrhythmic event, all terminated by ATP. A detailed time line of them is shown in figure 5. Patients 1, 4, and 5 were in primary and patient 9 in secondary prevention, their events occurred exclusively within the first year. Patient 2 experienced ATP for a fast VT after 63 months, at that time LVEF was 40%. Percutaneous coronary intervention was performed and, probably because of this, LVEF improved to 54% within the next 2 years. In patient 3, ATP was delivered for two episodes of ventricular tachycardia, the first at 9 months, the second at 40 months. At both times, LVEF was below 40%, which was its peak value anyway. In patient 6, ATP was delivered for two episodes of VT between months 30 and 42, when the current LVEF was unknown. In patients 7, 8 and 10, ATP was delivered for VT, although their LVEF was above 40%. Patients 9 and 10 were implanted for secondary prevention. Patient 9 had no further events after the first year, patient 10 had several events while his LVEF was >40%.

Thus the hypothesis of our study was refuted in 5/69 (7%) responder patients (patients 2/6/7/8/10). If the cut-offs for permanent improvement were 45% or 50%, only patient 8 is a misfit with hypothesis refutation rates of 2.4% and 5%, respectively.

Discussion

The main findings of this study are as follows. (1) Mean LVEF significantly improved from 25% at baseline to 34% at 1 year and remained stable over further 6 years. (2) Patients who improved to LVEF >40% were less likely to die during follow-up. (3) Patients who improved to LVEF

Table 1: Baseline characteristics of patients and predictors of improvement of left ventricular ejection fraction to >40%.

	All (n = 175)	Improved (n = 69)	Not improved (n = 106)	p-value univariable	p-value multivariable
Age	65 (SD 11)	65 (SD 11)	65 (SD 10)	0.84	
Body mass index	28 (SD 5)	27 (SD 5)	28 (SD 5)	0.44	
Female gender	26 (15%)	16 (23%)	10 (9%)	0.012	0.84
Primary prevention	141 (81%)	57 (83%)	84 (79%)	0.70	
Ischaemic cardiomyopathy	77 (44%)	30 (43%)	47 (44%)	1.00	
with CABG	37 (21%)	13 (19%)	24 (23%)	0.64	
Ejection fraction	25 (SD 6)	27 (SD 6)	24 (SD 5)	0.001	0.001
NYHA class					
II	42 (24%)	19 (27%)	23 (22%)	0.47	
III	118 (68%)	44 (64%)	74 70%)	0.41	
IV	14 (8%)	6 (9%)	8 (8%)	0.78	
Sinus rhythm	153 (87%)	64 (93%)	89 (84%)	0.10	
Left bundle-branch block	153 (87%)	63 (91%)	90 (85%)	0.25	
QRS width	161 (SD 23)	162 (SD 18)	160 (SD 25)	0.62	
Risk factors					
Renal failure	74 (42%)	26 (38%)	48 (45%)	0.32	
Hypertension	107 (61%)	43 (62%)	64 (60%)	0.43	
Diabetes	45 (26%)	18 (26%)	27 (25%)	0.46	
History of stroke	21 (12%)	10 (15%)	11 (10%)	0.32	
Chronic pulmonary disease	20 (11%)	9 (13%)	11 (10%)	0.39	
History of cancer	22 (13%)	9 (13%)	13 (12%)	0.45	
Vascular disease	24 (14%)	6 (9%)	18 (17%)	0.15	
Drug therapy at inclusion					
ACE Inhibitors / ARBs	173 (99%)	69 (100%)	104 (98%)	0.52	
Diuretics	154 (88%)	59 (86%)	95 (90%)	0.48	
Beta-blockers	151 (86%)	62 (90%)	89 (84%)	0.37	
Statins	99 (57%)	42 (61%)	57 (54%)	0.44	
Amiodarone	32 (18%)	7 (10%)	25 (24%)	0.03	0.02
Digoxin	19 (11%)	7 (10%)	12 (11%)	1.00	

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft;
NYHA = New York Heart Association; SD = standard deviation

>40% had significantly fewer arrhythmic events compared with those who did not. (4) The hypothesis of the study that patients in whom LVEF improves to >40% might have no ICD therapies beyond year one was refuted in 7%. (5) Apart from higher baseline LVEF, no meaningful predictor for LVEF improvement was identified.

The observation that mean improvement in LVEF mostly takes place in the first year and then remains stable is in line with other studies. Cleland et al. [3] showed a mean increase in LVEF of 7% (25 to 32%) from baseline to 18 months; Sutton et al. [25] a mean increase of 7% (24 to 31%) from baseline to 12 months. The current study shows an increase of 9%, extends this observation with a much longer follow-up period and adds the finding that the improvement remains stable in both groups of patients, in those with improvement to >40% as well as in those without improvement.

Our data confirm that patients whose LVEF improves to >40% have a reduced mortality with a cumulative 5-year survival of 95% (vs 73%, p <0.001). However, a direct comparison of these rates with the literature is not valid, as patients had to survive for 2 years in accordance with one of our several inclusion criteria [2, 3, 8, 26, 27].

In patients whose LVEF improves to >40% we showed highly significant reductions in first overall ICD therapies (p = 0.0001) and in first events in the VT zone (p = 0.0026), as well as a trend in first events in the VF zone (p = 0.07). Again, these findings are in line with several published registry studies. Data from our group showed that ICD interventions are very rare after the first year in patients with a primary prevention indication for CRT-D (1 in 46 patients) [15]. Itoh et al. demonstrated a decrease in VT/VF therapies (12% vs 31%, p = 0.03) in patients in whom left ventricular end-systolic volume (LVESV) decreased by >15% in a routine echo 6 months after implant. However, the early timing of LVESV determination and the fact that LVESV is in fact used to indicate response, but not necessity for ICD therapy, are considerable limitations of their results. Eickholt et al. [17] showed a decrease in ventricular arrhythmias in patients who responded to CRT, defined as a reduction of one NYHA class or an increase in LVEF of 10%, but did not use a cut-off that is deemed necessary for risk stratification [20]. Using data from the MADIT-CRT trial, Ruwald et al. [27] determined a rate as low as 5%

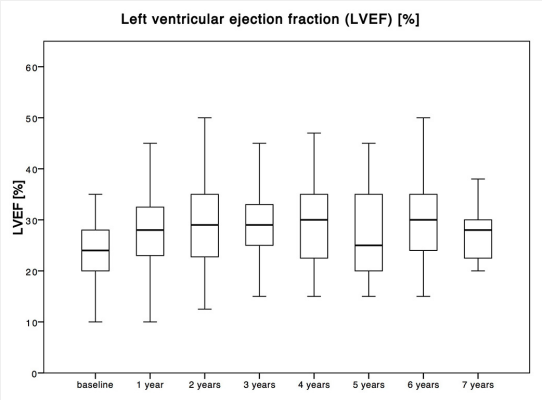

Figure 3

Changes in ejection fraction during long-term follow-up in patients without improvement to >40% (boxes indicate the interquartile range, whiskers 1.5-fold the length of the box).

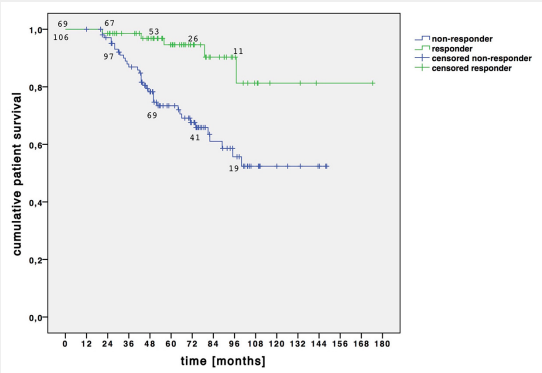

Figure 4

Kaplan-Meier curve of patient survival (NB: for inclusion into the study, patients had to survive for at least 2 years).

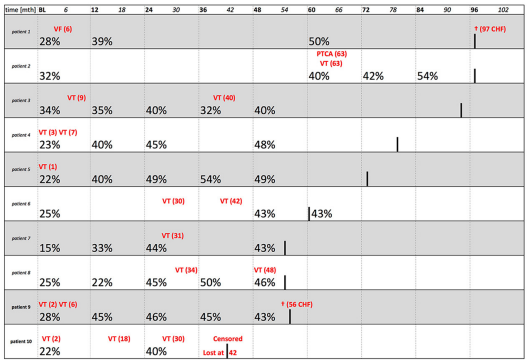

Figure 5

Time line of the 10 patients who improved to >40% and who had events.

Brackets indicate time from implantation in months. † = death; BL = baseline; CHF = congestive heart failure; VF = ventricular fibrillation; VT = ventricular tachycardia

Table 2: Rates of deaths and appropriate ICD therapies and point in time of events (shown as months after implant).

	All (n = 175)	Improved to >40% (n = 69)	Not improved (n = 106)	p value
Death	40 (23%)	5 (7%)	35 (33%)	<0.0001
Mean time to death	51 (SD 23)	59 (SD 30)	50 (SD 22)	
First ICD therapy	55 (31%)	10 (15%)	45 (43%)	0.0001
Mean time to first ICD therapy	21 (SD 21)	18 (SD 21)	21 (SD 21)	
First event in VF zone	17 (10%)	3 (4%)	14 (13%)	0.07
Mean time to first event in VF zone	21 (SD 18)	26 (SD 32)	20 (SD 16)	
First event in VT zone	38 (22%)	7 (10%)	31 (29%)	0.003
Mean time to first event in VT zone	20 (SD 22)	15 (SD 16)	22 (SD 24	

ICD = implantable cardioverter defibrillator; SD = standard deviation; VF = ventricular fibrillation; VT = ventricular tachycardia

appropriate ICD therapies in patients who improved their ejection fraction to >50%, all being terminated by ATP. The authors concluded that by using a CRT-D at the time of battery depletion "a risk of inappropriate ICD therapy is still present and these patients could be considered for downgrade from CRT-D to CRT-P at time of battery-depletion if no ventricular arrhythmias have occurred". A two-centre database study on super-responders (i.e. a persistent increase to >50%) was published by Zecchin et al. [19]. Seven percent of these patients had arrhythmias treated by their ICD (no data are shown on cycle length and type of ICD therapy), nullified by an inappropriate therapy rate of 8.5%. The amount of super-responders was remarkably high (24% compared with 7% in MADIT-CRT and 11% in our study).

A weakness of these studies (and hence a strength of our paper) is the fact that LVEF was usually determined early after implant and only once, thus disregarding further changes in LVEF as e.g. a subsequent decline after initial short-term improvement or persistent improvement in LVEF later during follow-up.

Applying the study results, downgrading a CRT-D to a CRT-P at the time of battery replacement may be discussed in patients with sustained improvement of LVEF to >40%. What could a patient gain or lose? They would not run a risk of inappropriate ICD therapy due to lead failure or supraventricular arrhythmias, but having VT episodes left untreated. Sebag et al. [18] showed that the annual rate of ICD therapy in patients who did not fulfil the ICD indication anymore (i.e. primary prevention, no arrhythmias, LVEF >40%) at the time of battery replacement was as low as 2.2%. Whether this can be considered as "low enough" to abstain from ICD backup has to be left to the interpretation of the treating cardiologist and the patient preference.

Strength and limitations

Our continuous collection of all available echocardiographic examinations and the long-term follow-up regarding LVEF evolution are the main strengths of this study. The number of patients included was small compared to studies from other high-volume centres but, on the other hand, follow-up duration was longer (5.5 ± 2.6 years). Other limitations are the retrospective study design and the lack of a standardised protocol for echocardiographic controls, which were not blinded and performed by different cardiologists. However, this resembles the real-life situation in which clinicians have to decide upon a CRT indication based exactly on such echocardiographic examinations and not on core laboratory data.

Conclusions

In 39% of CRT-D patients LVEF persistently improves to >40%. This is accompanied by a significantly lower risk of death and appropriate ICD therapies during follow-up. These patients might be considered candidates for device downgrading to CRT-P at the time of battery depletion.

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Figures (large format)

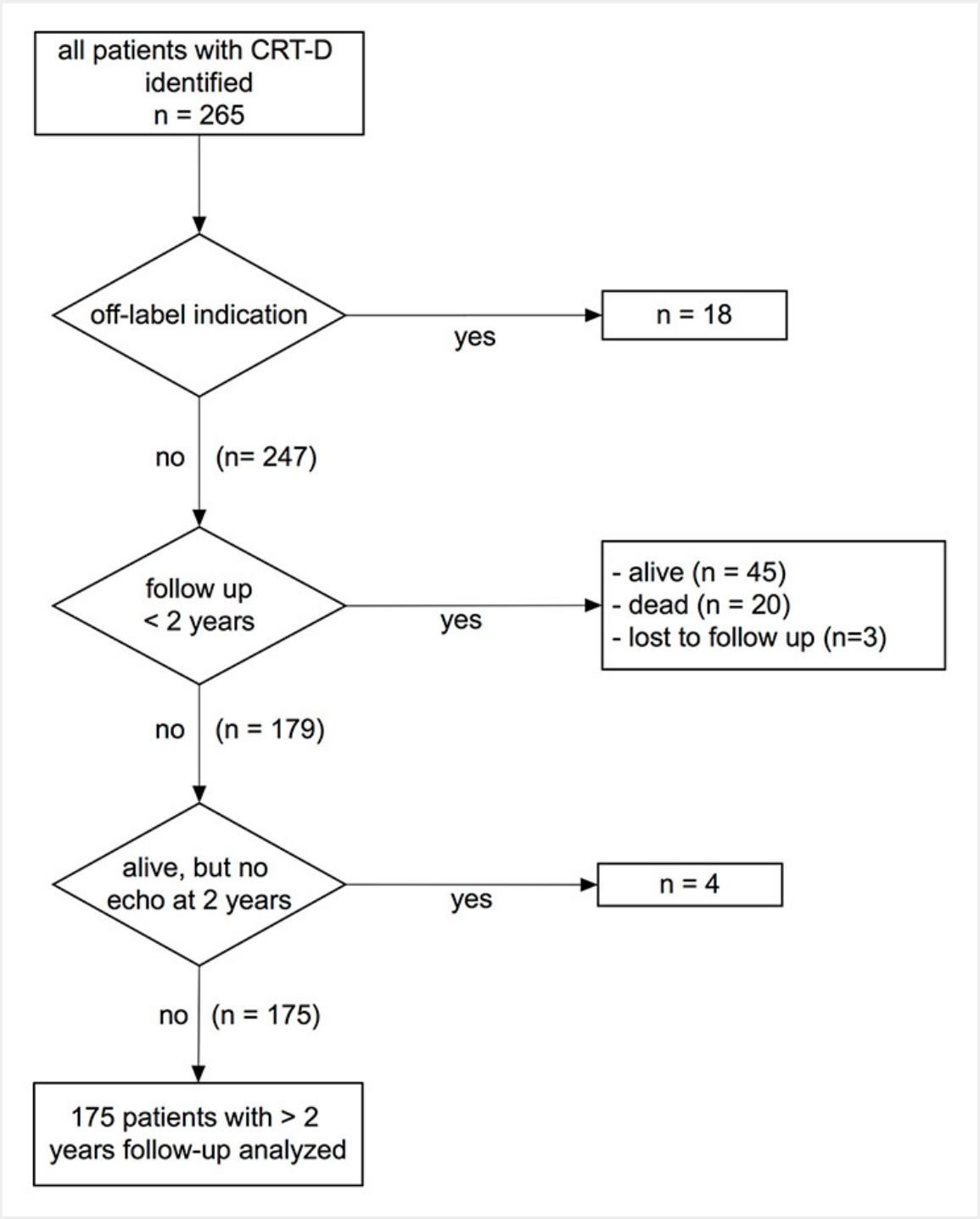

Figure 1

Flow-chart of all patients with a cardiac resynchronisation therapy with defibrillator back-up device (CRT-D) implanted at our hospital.

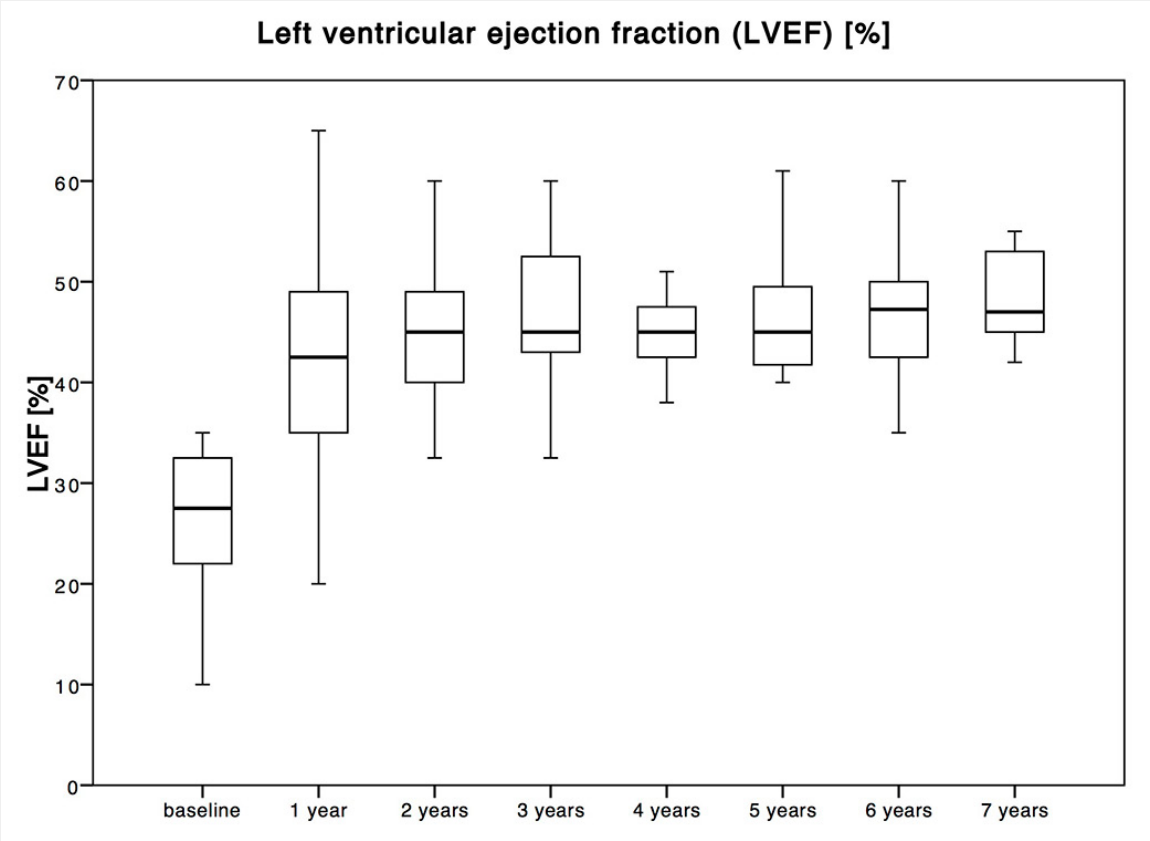

Figure 2

Changes in ejection fraction during long-term follow-up in patients with improvement to >40% (boxes indicate the interquartile range, whiskers 1.5-fold the length of the box).

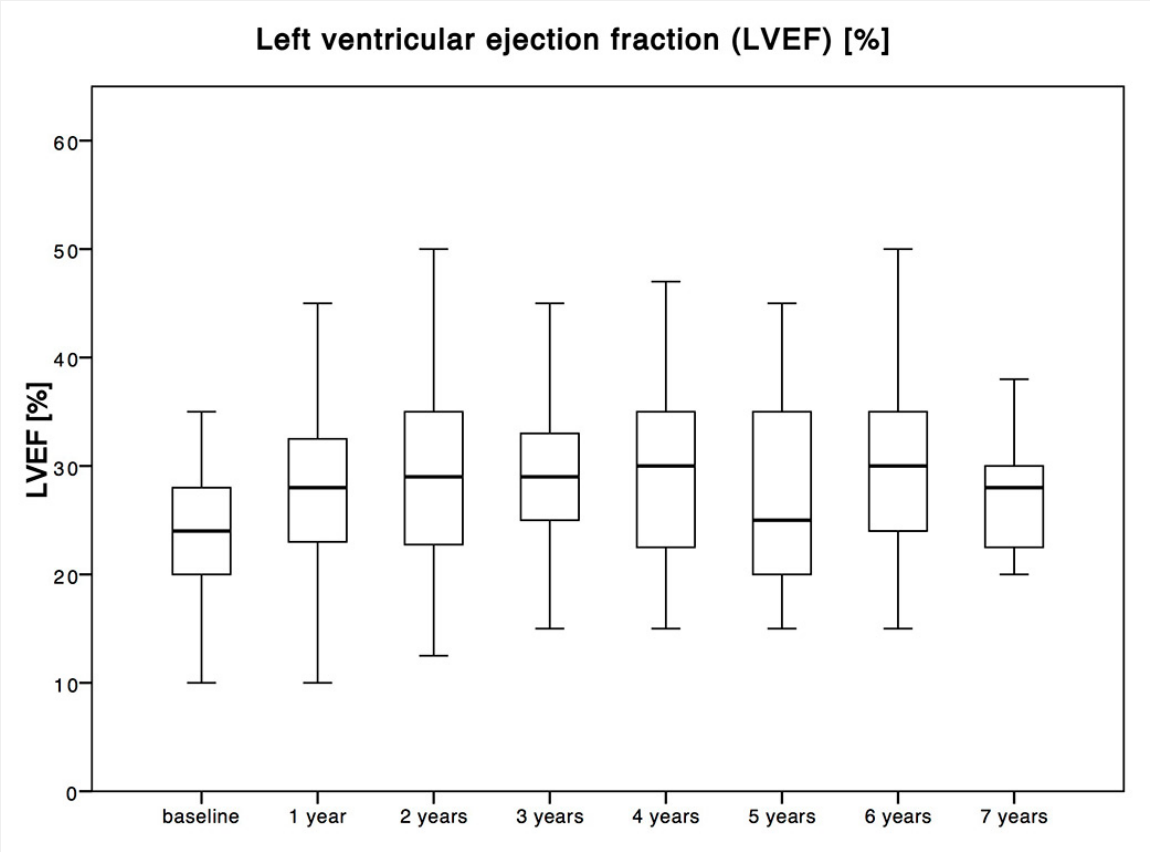

Figure 3

Changes in ejection fraction during long-term follow-up in patients without improvement to >40% (boxes indicate the interquartile range, whiskers 1.5-fold the length of the box).

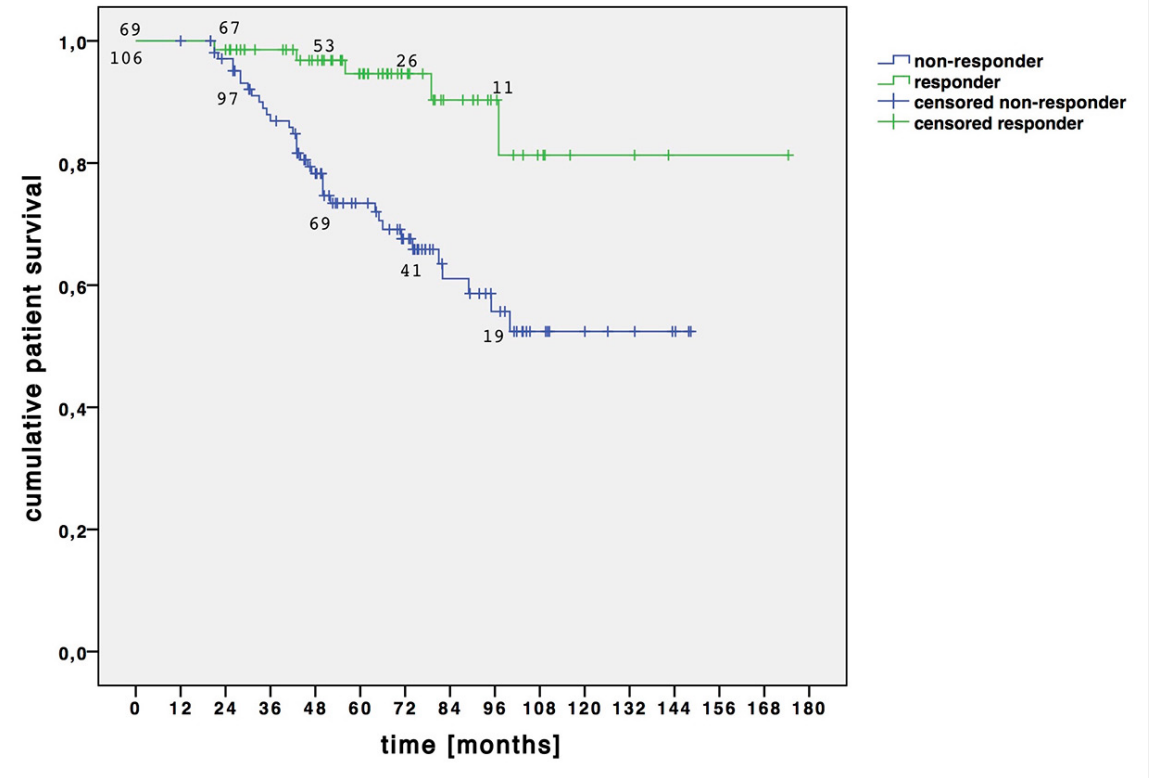

Figure 4

Kaplan-Meier curve of patient survival (NB: for inclusion into the study, patients had to survive for at least 2 years).

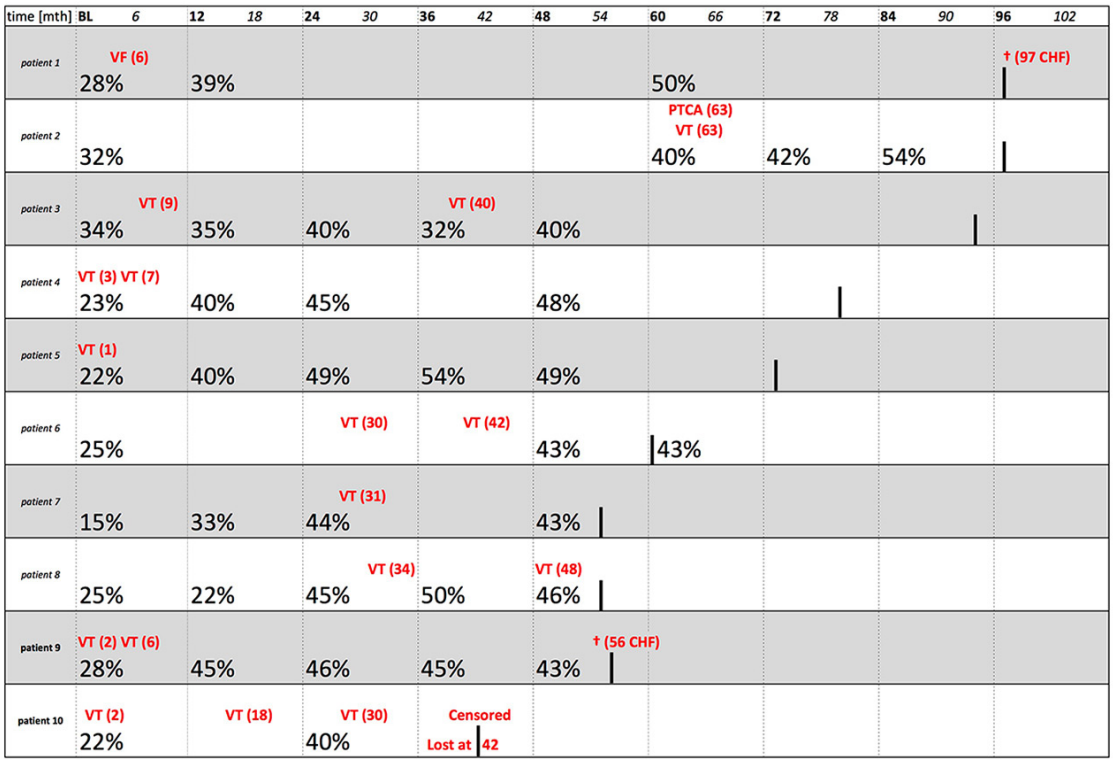

Figure 5

Time line of the 10 patients who improved to >40% and who had events.
Brackets indicate time from implantation in months. † = death; BL = baseline; CHF = congestive heart failure; VF = ventricular fibrillation; VT = ventricular tachycardia