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ORIGINAL ARTICLE

Early occurrence of heart failure hospitalization or ventricular arrhythmia re-define the long-term prognosis after CRT

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Abstract

Aims Classifying patients as responders or non-responders to cardiac resynchronization therapy (CRT) has been recently challenged, suggesting that preventing heart failure (HF) progression may also provide survival benefits. We assessed a novel classification based on echocardiographic left ventricular (LV) reverse remodelling and the occurrence of acute HF hospitalization (HHF) or sustained ventricular arrhythmia (VA) within 1-year post-CRT.

Methods and results Patients implanted with a CRT defibrillator (CRT-D) at our department between 2010 and 2020 were classified based on the change in LV ejection fraction (LVEF) within 1 year as responders (increase $\geq$ 10%), non-progressors (increase $<$10%) or progressors (decline). Patients in each category were further divided based on the occurrence or absence of an HHF/VA event within 1-year post-implantation. Long-term survival free of heart transplantation or LV assist device implantation was calculated for all six subgroups. Cohorts demonstrating no significant between-group differences were grouped together and reclassified as improved, stabilized or worsened. One hundred nineteen responders, 79 non-progressors and 69 progressors were identified based on the echocardiographic response. Long-term event-free survival was higher for responders as compared with non-progressors (hazard ratio [HR] 0.51, $P = 0.002$) or progressors (HR 0.34, $P < 0.0001$). Furthermore, non-progressors had better outcome than progressors (HR 0.63, $P = 0.03$). Long-term prognosis in patients was superior with versus without an HHF/VA event within each group of responders (HR 0.47, $P = 0.03$), non-progressors (HR 0.31, $P = 0.0001$) or progressors (HR 0.38, $P = 0.0004$). No survival difference was found between responders and non-progressors with no event (HR 0.69, $P = 0.09$), who were recategorized as improved. Long-term prognosis was also similar in responders with any event and in progressors with no event (HR 0.98, $P = 0.88$; stabilized), as well as in non-progressors and progressors with any event (HR 0.87, $P = 0.63$; worsened). Median survival rates demonstrated significant differences between the improved, stabilized and worsened groups (102.3, 62.0 and 24.4 months; HR 0.53, $P = 0.006$ between improved and stabilized; HR 0.41, $P < 0.0001$ between stabilized and worsened; HR 0.21, $P < 0.0001$ between improved and worsened cohorts, respectively).

Conclusions Long-term survival can be predicted based on the change in LVEF and on the occurrence of an HHF/VA event within 1-year after CRT-D implantation. Stabilized patients have significantly better prognosis as compared with the worsened group. Patients with strikingly poor prognosis can be identified using this assessment method.

Keywords Cardiac resynchronization therapy (CRT); CRT non-responder; non-progressor; progressor

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Introduction

Cardiac resynchronization therapy (CRT) induces reverse left ventricular (LV) remodelling, improves heart failure (HF) symptoms and functional capacity and reduces HF-related mortality and hospitalization. However, no definite improvement can be demonstrated in approximately one third of HF patients, who have traditionally been referred to as CRT non-responders (CRT NR).[1, 2] With no widely accepted definition of CRT NR, various outcome measures have been used in different studies.[3–6] These include the change in echocardiographic parameters such as the left ventricular ejection fraction (LVEF) or the left ventricular end-systolic volume index (LV ESVi) measured before and usually 6–12 months after device implantation. The signs of LV reverse remodelling indicated by the improvement in these parameters demonstrated significant correlation with the prognosis of CRT recipients in many investigations,[5, 7] while functional improvement as assessed by the changes in New York Heart Association (NYHA) functional class, the results of the 6-min walk test and quality of life questionnaire showed a weaker correlation with hard endpoints such as hospitalization for heart failure (HHF) and mortality.[8–11] Further, the agreement between the different measures used to assess the response to CRT is remarkably poor: LV reverse remodelling showed variable correlation to the degree of symptomatic and functional improvement in many studies.[4, 5, 12, 13]

In addition to the lack of a consensus on the method of assessment and on the definition of the response to CRT, the concept to categorize CRT recipients as responders or non-responders has recently been challenged.[14, 15] As HF is a progressive disease, patients may still derive significant clinical benefit from a medical intervention which stops or slows disease progression even in the absence of definite signs of improvement. In line with this concept, Steffel and Ruschitzka proposed a more comprehensive classification of possible clinical courses after CRT implantation including two categories of improvement (responders and super-responders), two categories of decline (non-responders and negative responders) and a category for patients with neither improvement nor worsening who were called non-progressors.[16] A joint position statement from the Heart Failure Association of the European Heart Rhythm Association, the European Association of Cardiovascular Imaging and the European Society of Cardiology called to stop the binary approach of CRT response and suggested to view CRT as a modifier of the clinical course of HF. Further, this position paper supported the use of Packer's hierarchical scoring system which considers the lack of mortality, the lack of hospital admission for HF and stable functional status without additional diuretic use.[17, 18] This scoring system referred to as clinical composite score (CCS) also acknowledges stability (the lack of deterioration) as a positive outcome after CRT.

This more detailed classification of CRT response in the context of survival was used in recent publications.[7, 14, 19] Despite the differences in the definitions and in the methods used to assess CRT response (changes in LV ESVi, LVEF or CCS), a relative benefit of the therapy in stabilized or non-progressor patients were demonstrated in all these studies.

Herein, we applied a novel assessment scheme to categorize the response to resynchronization based on parameters which are readily available during the routine follow-up (FU) of patients after CRT: (1) echocardiographic signs of LV reverse remodelling and (2) the occurrence of a clinical event, either hospitalization for acute HF (HHF) or a sustained ventricular arrhythmia (VA) episode. We evaluated the predictive value of these measures for long-term mortality in patients who underwent the implantation of a CRT device with defibrillator function (CRT-D).

Methods

Study population and design

This was a single-centre, retrospective study including all patients who underwent *de novo* implantation of a CRT-D device for HF with reduced EF (HFrEF) and both primary and secondary prevention indication for VAs at our department between 1 January 2010 and 31 December 2019. All patients possessed with a minimum of 12-month survival and were followed up to 31 December 2022. The indications for CRT-D implantation were in line with contemporary guidelines of the European Society of Cardiology (ESC). The study protocol was approved by the ethics committee of the University of Debrecen (Registry number: BMEÜ/4388-1/2022/EKU) and the study complied with the Declaration of Helsinki. All patients received guideline-directed optimized medical therapy (OMT) for HF before and after CRT implantation.

CRT-D implantations were performed according to standard practice. LV pacing leads were inserted in the coronary sinus, preferably in the lateral or posterolateral veins. ICD programming for VA detection and treatment is based on the 'HRS/EHRA/APHRS/LAHRS 2015 and 2019 expert consensus statement on optimal implantable cardiac defibrillator programming and testing'. Patients were evaluated before the implantation and thereafter at 6 weeks, 6 and 12 months at our outpatient clinic during the first year and subsequently at every 6–12 months. At each FU, 12-lead ECG, 2D echocardiography, device interrogation and NYHA functional class evaluation were performed. Echocardiographic measurements included left atrial diameter, LV end-systolic- and end-diastolic diameters and LVEF using the modified Simpson biplane method. Patients who failed to attend the first year FU visit for any reason were excluded from the analysis.

Baseline patient characteristics including age, gender, pre- and postoperative LVEF and NYHA functional class, baseline and postoperative QRS durations, the ratio of non-LBBB QRS morphology, body mass index (BMI, kg/m^2), aetiology of HF, rate of hypertension, diabetes mellitus (DM), atrial fibrillation (AF), previous stroke/transient ischaemic attack (TIA) and major laboratory parameters (creatinine and haemoglobin levels) were recorded. Moreover, clinical events including HHF or ICD activity (an appropriate shock or anti-tachycardia pacing recovered from device memory) for a sustained VA episode (either sustained ventricular tachycardia or ventricular fibrillation) were collected within 1-year pre- and post-implantation.

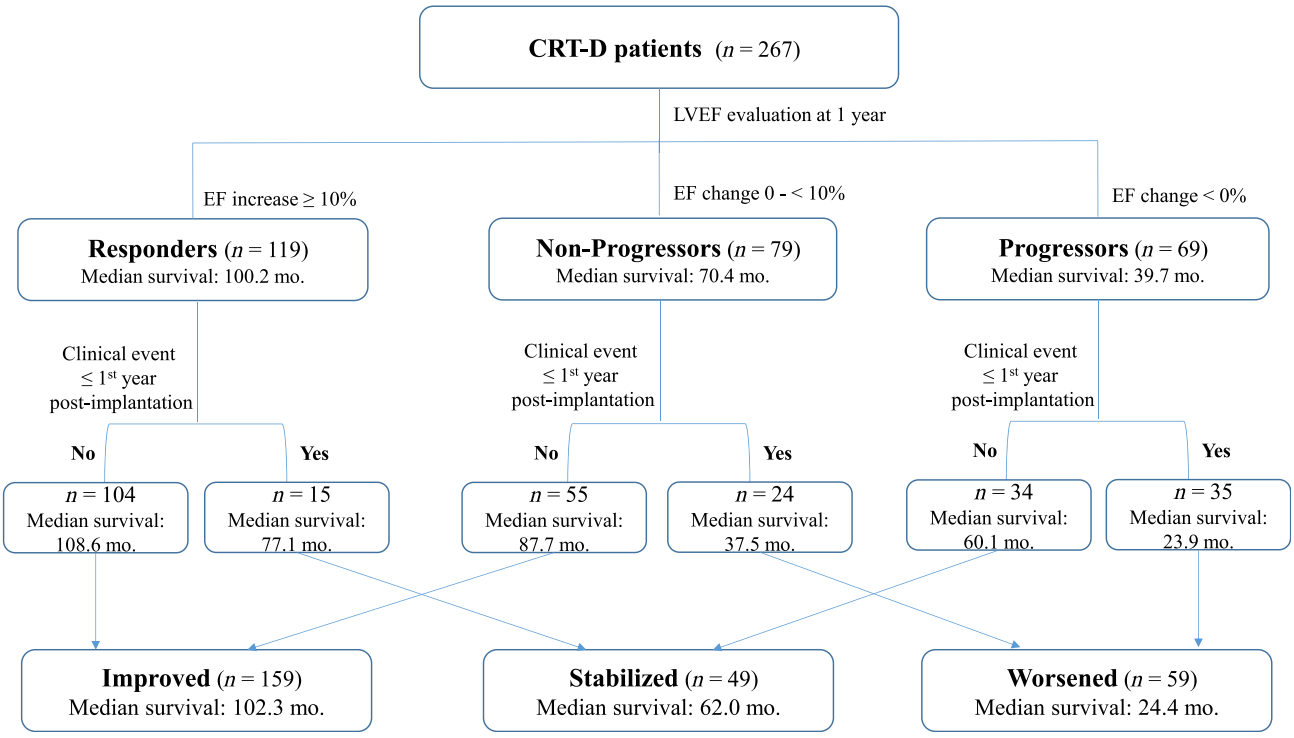
Patient subgroups and study endpoint

As the first step, the echocardiographic response to CRT was assessed based on the absolute change in LVEF at the 12-month FU. Patients were assigned to three categories: (1) *responders*: patients demonstrating a minimum 10% increase in the LVEF, (2) *non-progressors*: patients with a less than 10% improvement in LVEF and (3) *progressors*: patients with a decline in LVEF.

As the second step, the subgroups of CRT responders, non-progressors and progressors were further divided based on the occurrence or absence of a clinical event, either HHF or sustained VA, recorded by the ICD during the first year after the device implantation (*Figure 1*). Additionally, HHF and VA events were also evaluated within 1 year before the CRT implantation.

The primary endpoint was the composite of all-cause mortality, heart transplantation (HTX) or left ventricular assist device (LVAD) implantation determined at the end of FU. Survivals free of these endpoints were calculated for all the three groups based on echocardiographic changes as well as for the 6 subgroups categorized according to both the echocardiographic response and the occurrence of a clinical event. Patients with similar survival rates in the six subgroups were then grouped together thereby creating three novel cohorts of improved, stabilized or worsened after recategorization. Baseline characteristics, comorbidities and long-term survival in these new groups were compared.

Figure 1 Flow chart demonstrating categorization of CRT-D patients. Patients were grouped as responders, non-progressors and progressors based on the change in LVEF at 1-year post-implantation. Each group was then dichotomized considering the occurrence of at least one clinical event within 1 year after device implantation. Finally, patients demonstrating similar long-term survival rates in the six subcohorts were grouped together and reclassified as improved, stabilized or worsened (clinical event = hospitalization for heart failure or sustained ventricular arrhythmia. See text for further details).



Statistical analysis

GraphPad Prism 10 (GraphPad Software Inc., La Jolla, CA, USA) and SPSS Statistics (IBM SPSS Statistics) were applied for statistical analysis. Continuous variables were depicted with mean and standard error of mean (SEM), categorical variables were illustrated by counts and percentages. Survival analyses were calculated by Kaplan–Meier estimates and log-rank test. Univariate Cox regression analysis was used to identify the individual factors related to patient survival, while multivariate Cox regression (forward stepwise LR method) evaluated the independent prognostic factors. Group comparisons were performed by Student *t*-test, Mann–Whitney *U*-test and Kruskal–Wallis test for continuous variables. Chi-square distribution was used for evaluating the categorical variables. Paired Student's *t*-test was carried out to compare the changes in variables from baseline to the data obtained at first year FU in each group. *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 267 patients with HFrEF underwent de novo CRT-D implantation during the study period with a minimum of 12-month survival (*Table* 1) for primary (248 patients; 92.9%) and for secondary prevention (19 patients; 7.1%) indication. One hunded nineteen patients were categorized as responders, 79 as non-progressors and 69 as progressors based on the change in LVEF by the end of the first year (*Figure 1*). The three groups demonstrated no significant differences in age, sex, preoperative functional class, pre-CRT HHF/VA events and QRS duration. Non-LBBB QRS morphology was the most prevalent in progressor patients. Progressors had higher LVEF before the implantation than responders ($P = 0.02$). The magnitudes of change in LVEF 1-year post-implantation demonstrated per definitionem differences in the three response categories. Post-implantation functional status showed significant differences in the three groups with the best and the worst values in responders and in progressors, respectively. Similarly, the magnitudes of change in QRS durations after resynchronization (ΔQRS) were statistically significant: the largest decrease in magnitude was observed in responders, while the smallest in progressors. Regarding comorbidities, no significant differences were observed in HF aetiology, hypertension, serum creatinine and haemoglobin levels and BMI between the three cohorts. DM was less prevalent in CRT responders as compared with non-progressors and progressors. AF and previous stroke/TIA were significantly more prevalent in progressor patients.

Guideline-dictated medical treatment was similar in the three patient groups except for the use of diuretics, which

Table 1 Baseline characteristics of echocardiographic responder, non-progressor and progressor patients.

	Responder (I) ($n = 119$)	Non-progressor (II) ($n = 79$)	Progressor (III) ($n = 69$)	*P*-value		
				I vs. II	I vs. III	II vs. III
Age, years, mean ± SEM	62.4 ± 1.0	60.8 ± 1.3	61.4 ± 1.2	0.35	0.54	0.71
Male gender, *n* (%)	96 (80.7)	70 (88.6)	63 (91.3)	0.17	0.06	0.79
Preop. LVEF, %, mean ± SEM	26.0 ± 0.6	26.6 ± 0.6	28.1 ± 0.6	0.51	**0.02**	0.086
Preop. NYHA, *n* (%)						
1	1 (0.8)	1 (1.3)	2 (2.9)	0.72	0.24	0.74
2	35 (29.4)	25 (31.6)	19 (27.5)			
3	72 (60.5)	49 (62.0)	46 (66.7)			
4	11 (9.2)	4 (5.0)	2 (2.9)			
Preop. QRS duration, ms, mean ± SEM	155.4 ± 1.7	156.0 ± 2.3	154.5 ± 2.3	0.82	0.74	0.63
Baseline non-LBBB, *n* (%)	37 (31.1)	25 (31.6)	32 (46)	0.93	**0.04**	0.07
Preop. HHF/VA, *n* (%)	67 (56)	41 (52)	38 (55)	0.54	0.87	0.70
Postop. LVEF, %, mean ± SEM	41.2 ± 0.7	30.5 ± 0.6	22.6 ± 0.7	**<0.0001**	**<0.0001**	**<0.0001**
Postop. NYHA at 1-year, *n* (%)						
1	28 (23.5)	8 (10.1)	2 (2.9)	**<0.0001**	**<0.0001**	**0.014**
2	87 (73.1)	53 (67.1)	35 (50.7)			
3	4 (3.4)	16 (20.3)	29 (42.0)			
4	0 (0)	2 (2.5)	3 (4.3)			
Postop. QRS duration, ms, mean ± SEM	129.2 ± 1.4	136.0 ± 1.9	142.7 ± 2.3	**0.003**	**<0.0001**	**0.023**
ΔQRS, ms, mean ± SEM	−26.2 ± 1.5	−20.1 ± 2.0	−11.7 ± 1.8	**0.01**	**<0.0001**	**0.003**
Ischaemic aetiology, *n* (%)	69 (58.0)	44 (55.7)	37 (53.6)	0.77	0.65	0.87
Hypertension, *n* (%)	67 56.3)	42 (53.2)	40 (58.0)	0.77	0.88	0.62
Diabetes mellitus, *n* (%)	32 (26.9)	35 (44.3)	29 (42.0)	**0.01**	**0.04**	0.86
Creatinine (μmol/L), mean ± SEM	93.3 ± 2.5	101.0 ± 3.8	98.1 ± 3.8	0.08	0.28	0.59
AF, *n* (%)	22 (18.5)	16 (20.3)	22 (31.9)	0.85	**0.03**	0.08
Stroke/TIA, *n* (%)	6 (5.0)	5 (6.3)	12 (17.4)	0.85	**0.009**	**0.04**
BMI, kg/m^2, mean ± SEM	29.0 ± 0.5	29.2 ± 0.6	29.3 ± 0.6	0.67	0.62	0.94

Values in bold illustrate *P*-values with statistical significance.

was the lowest in CRT responders and the highest in progressors (*Table S1*). Of note, sodium-glucose cotransporter-2 inhibitor (SGLT-2i) medication was not available in our country during the study period with HFrEF indication.

Long-term prognosis of responder, non-progressor and progressor patients

Total FU durations (months; mean ± SEM) were 69.7 ± 3, 46.0 ± 3.2 and 41.9 ± 3.7 months in echocardiographic responders, non-progressors and progressors, and HTX/LVAD-free survival rates were 68.1%, 46.8% and 40.3%, respectively. Kaplan–Meier analysis demonstrated estimated median survival of 100.2, 70.4 and 39.7 months in the three groups (*Figure 1* and *Figure 2*). The cumulative probability of HTX- or LVAD-free survival of responders was significantly higher as compared with either non-progressors ($P = 0.002$) or progressors ($P < 0.0001$). The difference between non-progressors and progressors was also significant ($P = 0.03$).

Hospitalizations for acute HF and/or sustained VA during the first year post-implantation

At least one event of HHF or VA occurred in 15 (12.6%), 24 (30.4%) and 35 (50.7%), patients during the first year after device implantation in the responder, non-progressor and progressor groups, respectively. In responders, clinical events predominantly consisted of only VAs (60%), while there was a preponderance of HHF alone (65.7%) or in association with VAs (22.9%) in progressors (*Figure* S1). Inappropriate ICD activity occurred in in 5 (4.2%), 4 (5.1%) and 3 (4.3%) patients during the first year after device implantation in responders, non-progressors and progressors ($P > 0.05$).

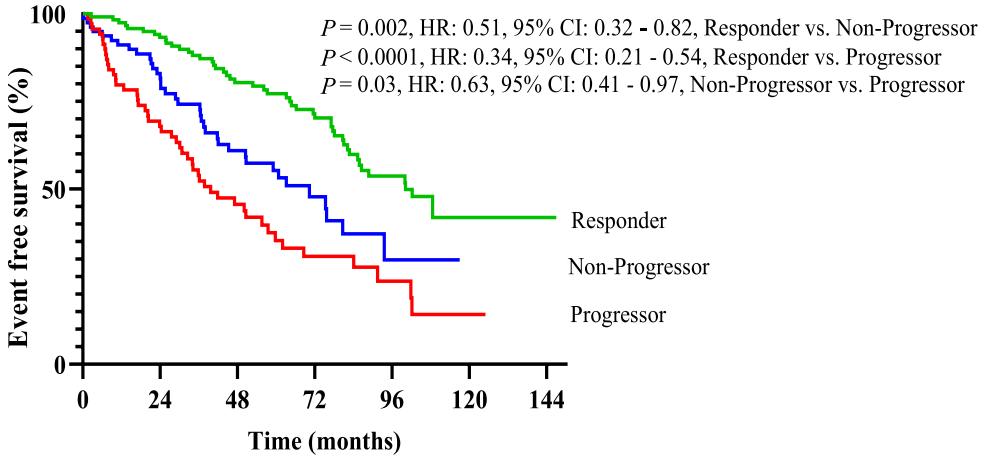
Patients with any HHF/VA events within 1-year post-implantation had significantly worse long-term prognosis as compared with those without any clinical episode. The prognosis was irrespective of the type of clinical events, as demonstrated by comparable outcomes for patients with only HF, only VA episodes or both within 1-year post-implantation (Figure S2A,B).

Furthermore, the details of VA events and ICD activity were also predictive for the long-term prognosis. As demonstrated by the Kaplan–Meier survival curve (Figure S2C,D) patients with multiple VA events requiring both ATP and shock episodes had strikingly poor prognosis. Interestingly, patients with VA events necessitating only ATP episodes had comparable outcome to those without VA events. VAs terminated by ICD shocks were associated with unfavourable prognosis compared to those terminated by only ATPs or patients with no VA episodes.

Long-term prognosis of patients based on both echocardiographic response and HHF/VA events during the first year after device implantation

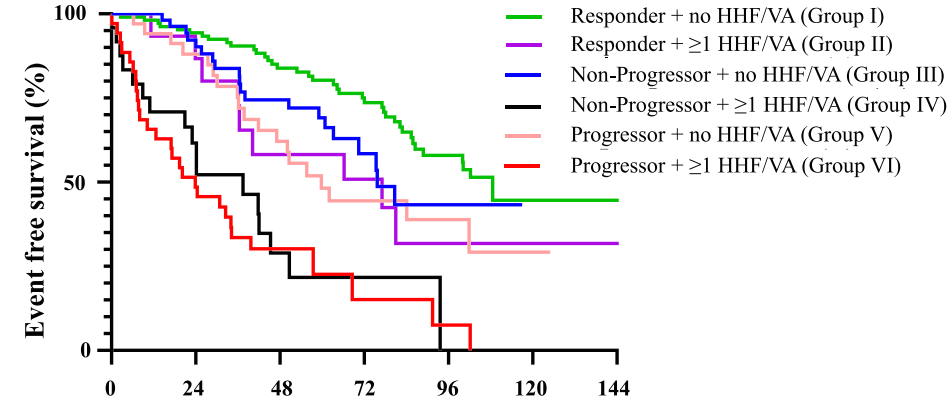
Kaplan–Meier modelling was used to predict long-term HTX/LVAD-free survival in thesix patient cohorts categorized

Figure 2 Long-term survival free of all-cause death, HTX or LVAD implantation in responders, non-progressors and progressors based on the change in LVEF data at 12 months FU.



Number at risk							
Responder	119	112	80	60	29	7	2
Non-Progressor	79	58	35	16	5	1	1
Progressor	69	46	26	13	7	2	1

Figure 3 Long-term survival free of all-cause death, HTX or LVAD implantation in the 6 subgroups categorized according to both the echocardiographic response and the occurrence of an HHF/VA event during the first year after device implantation. (see median survival rates and the results of statistical comparisons in *Figure 1* and *Table 2*).



Number at risk							
Group I.	104	101	73	55	28	6	2
Group II.	15	14	9	8	3	3	3
Group III.	55	45	31	14	5	1	1
Group IV.	24	14	5	3	1	1	1
Group V.	34	29	20	11	6	1	0
Group VI.	35	18	7	3	2	0	0

Table 2 Statistical analysis of long-term survival free of all-cause death, HTX or LVAD implantation in the six subgroups categorized according to both the echocardiographic response and the occurrence of an HHF/VA event during the first year after device implantation.

	P-value	Hazard ratio	CI	Median survival (mo.)
I vs. II	**0.03**	0.47	0.18–1.21	108.6 vs. 77.1
III vs. IV	**0.0001**	0.31	0.14–0.68	87.7 vs. 37.5
V vs. VI	**0.0004**	0.38	0.21–0.69	60.1 vs. 23.9
I vs. III	0.09	0.69	0.35–1.15	108.6 vs. 87.7
II vs. V	0.88	0.98	0.45–2.19	77.1 vs. 60.1
IV vs. VI	0.63	0.87	0.48–1.56	37.5 vs. 23.9

Upper panel: Comparison of patients with versus without a HHF/VA event demonstrates significant differences in all three groups of patients classified according to LVEF change at 1-year post-implantation. Lower panel: Groups demonstrating similar long-term survival with no statistical significance. I: responder with no HHF/VA, II: responder with any HHF/VA, III: non-progressor with no HHF/VA, IV: non-progressor with any HHF/VA, V: progressor with no HHF/VA, VI: progressor with any HHF/VA; HHF = hospitalization for heart failure; VA = sustained ventricular arrhythmia; see also *Figure* 3. Values in bold illustrate *P*-values with statistical significance.

based on both the LVEF response and the occurrence of HHF/VA event during the first year after the implantation (*Figures 1* and *3*). Long-term prognosis in patients with no HHF/VA event was superior as compared with those having any episode within each group of responders, non-progressors or progressors, respectively (*Table 2*, upper panel).

No significant difference in long-term survival was found between responders with no event and in non-progressors with no event; these patients were recategorized as improved. Long-term prognosis was also similar in responder patients with any event and in progressors with no event during the first year, these patients were recategorized and stabilized. Finally, non-progressor and progressor patients with any event demonstrated no statistical difference in long-term prognosis and were thereby recategorized as worsened (*Table 2*, lower panel). Median survival rates showed significant differences between these three reclassified groups of patients: 102.3 months for the improved, 62.0 months for the stabilized and 24.4 months for the worsened cohort (*Figures 1 and 4*).

Comparison of clinical variables in the 3 groups of patients categorized as improved, stabilized and worsened is shown in *Table 3*. Postoperative functional class was significantly different between the 3 cohorts, while post-implantation LVEF, QRS duration and ΔQRS demonstrated the most favourable

values in improved patients with no significant difference between the stabilized and the worsened cohorts. Worsened patients had the highest ratio of pre-operative non-LBBB ECG morphology. The prevalence of comorbidities was similar in the three groups except for DM and AF, which were more prevalent in worsened than in improved patients.

Figure 4 Long-term survival free of all-cause death, HTX or LVAD implantation in patients recategorized as improved, stabilized and worsened. Kaplan–Meier modelling demonstrates three distinct survival curves with significant differences.

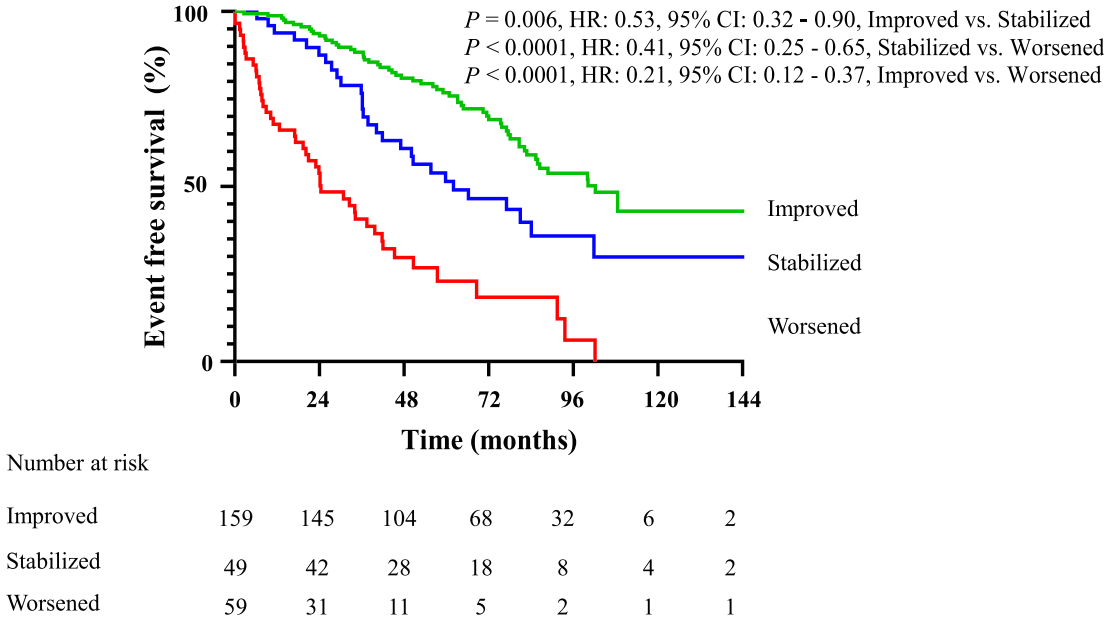


Table 3 Baseline characteristics of improved, stabilized and worsened patients

	Improved (I) (n = 159)	Stabilized (II) (n = 49)	Worsened (III) (n = 59)	*P*-value		
				I vs. II	I vs. III	II vs. III
Age, years, mean ± SEM	61.3 ± 0.9	62.8 ± 1.3	61.6 ± 1.4	0.41	0.84	0.55
Male gender, *n* (%)	129 (81.8)	44 (89.8)	56 (94.9)	0.19	**0.01**	0.46
Preop. LVEF, %, mean ± SEM	26.6 ± 0.5	26.9 ± 0.8	27.1 ± 08	0.77	0.58	0.84
Preop. NYHA, *n* (%)						
1	1 (0.6)	2 (4.1)	1 (1.7)	0.34	0.32	0.48
2	51 (32.1)	14 (28.6)	14 (23.7)			
3	96 (60.4)	29 (59.2)	42 (71.2)			
4	11 (6.9)	4 (8.2)	2 (3.4)			
Preop. QRS duration, ms, mean ± SEM	155.4 ± 1.5	158.0 ± 3.1	152.6 ± 2.3	0.42	0.32	0.16
Baseline non-LBBB, *n* (%)	46 (28.9)	19 (38.8)	27 (45.8)	0.18	**0.004**	0.15
Preop. HHF/VA, *n* (%)	83 (52)	29 (59)	33 (56)	0.35	0.33	0.12
Postop. LVEF, %, mean ± SEM	38.2 ± 0.7	28.1 ± 1.4	25.2 ± 0.9	<**0.0001**	<**0.0001**	0.09
Postop. NYHA at 1-year, *n* (%)						
1	33 (20.8)	5 (10.2)	0 (0.0)	**0.003**	<**0.0001**	**0.002**
2	113 (71.1)	31 (63.3)	28 (16.9)			
3	13 (8.2)	13 (22.0)	26 (44.1)			
4	0 (0.0)	0 (0.0)	5 (8.5)			
Postop. QRS duration, ms, mean ± SEM	130.6 ± 1.2	141.5 ± 3.0	140.0 ± 2.2	<**0.0001**	<**0.0001**	0.68
ΔQRS, ms, mean ± EM	−24.8 ± 1.3	−17.3 ± 4.0	−12.9 ± 1.9	**0.02**	<**0.0001**	0.3
Ischaemic aetiology, *n* (%)	92 (57.9)	28 (57.1)	30 (50.8)	>0.99	0.36	0.56
Hypertension, *n* (%)	90 (56.6)	30 (61.2)	29 (49.2)	0.62	0.36	0.25
Diabetes mellitus, *n* (%)	48 (30.2)	17 (34.7)	28 (47.5)	0.60	**0.04**	0.33
Creatinine (μmol/L), mean ± SEM	95.2 ± 2.4	98.5 ± 4.0	100.0 ± 4.4	0.49	0.31	0.81
AF, *n* (%)	24 (15.1)	8 (16.3)	19 (32.2)	0.82	**0.007**	0.07
Stroke/TIA, *n* (%)	9 (5.7)	6 (12.2)	8 (13.6)	0.13	0.08	>0.99
BMI, kg/m^2, mean ± SEM	28.9 ± 0.4	29.8 ± 0.6	29.2 ± 0.6	0.27	0.71	0.50

Values in bold illustrate *P*-values with statistical significance.

Predictors of unfavourable clinical outcome

Univariate and multivariate Cox-regression analyses were performed using the baseline clinical characteristics including demographics, comorbidities, patients' status based on LVEF response and the occurrence of HHF/VA events at 1-year and within first year in the overall CRT-D population. Based on univariate Cox-regression analysis, predictors for unfavourable clinical outcome included the occurrence of HHF/VA within 1-year pre- and post-implantation, progressor status at 1-year FU, age >75 years, renal insufficiency, ΔQRS <10 ms, non-LBBB ECG morphology and baseline NYHA III–IV functional class. In contrast, favourable outcome was predicted by responder status at 1-year and by a decrease in QRS duration exceeding 20 ms. With multiple Cox regression analysis, only echocardiographic responder status at 1-year predicted the favourable clinical outcome; however, an HHF/VA event within 1-year pre- and post-implantation, age >75 years, renal insufficiency, ΔQRS <10 ms and non-LBBB QRS morphology were identified as independent predictors of poor prognosis in the overall CRT-D population (*Table 4*).

Discussion

A better understanding of the correlation between the initial response to CRT and the longer-term outcomes is important to recognize the need for therapy escalation and to provide patients with precise prognostic information. It has been a general practice since the introduction of CRT into clinical practice to classify patients as either responders or non-responders. However, this approach does not consider the progressive nature of HF and the potential benefit of CRT in suspending or slowing deterioration even in the absence of measurable improvement at initial assessment after device implantation. Categorizing 30%–40% of CRT patients as non-responders contributed to a false perception of both patients and the medical community regarding the clinical value of the therapy.[17]

In this research, we categorized patients based on the magnitude of reverse remodelling and on the occurrence of two clinical events, HHF and VA within 12 months post-implantation. Considering solely the echocardiographic response, patients were initially classified as responders, non-progressors or progressors with three distinct Kaplan–Meier survival curves confirming previous observations that the presence or absence of LV reverse remodelling is a significant predictor of the outcome after CRT.[7, 12, 19–21] Our results also support the concept that patients who demonstrate neither significant improvement nor deterioration represent a distinct category with better prognosis than those showing progressive impairment of LV function.[14, 20, 22] The three cohorts classified according to echocardiographic changes were then further dichotomized based on the occurrence of a clinical event, either HHF or a sustained VA episode recorded in the ICD memory. Comparison of the long-term survival curves in the 6 groups demonstrated that the occurrence of a clinical event predicted a significantly worse prognosis within each group classified according to pure echocardiographic response. Moreover, a significant overlap in survival was shown between the initially classified cohorts: responders and non-progressors with no clinical event had comparable prognosis, as well as responders with any and progressors with no clinical event. Reclassifying patients using this composite measure that combines the remodelling response and the clinical endpoints, three cohorts with homogenous within-group prognosis could be formed: improved, stabilized

Table 4 Univariate (left panel) and multivariate (right panel) Cox-regression analysis of the overall CRT-D population for long-term survival free of LVAD and HTX

	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
HHF/VA within 1-year pre-impl.	1.50	1.06–2.10	**0.023**	1.75	1.29–2.62	**0.01**
HHF/VA within 1-year post-impl.	3.43	2.39–4.92	<**0.001**	2.17	1.92–4.21	<**0.001**
Progressor status at 1-year	2.38	1.66–3.41	<**0.001**			
Non-progressor status at 1-year	0.88	0.66–1.41	0.116			
Responder status at 1-year	0.42	0.289–0.60	<**0.001**	0.45	0.33–0.71	<**0.001**
Male gender	1.16	0.68–1.99	0.582			
Age < 65	0.95	0.67–1.33	0.752			
Age 65–75	0.83	0.58–1.19	0.302			
Age > 75	2.49	1.44–4.27	**0.001**	2.20	1.61–5.00	<**0.001**
Renal insufficiency	2.07	1.46–2.93	<**0.001**	1.78	1.18–2.40	**0.004**
Diabetes mellitus	1.20	0.84–1.70	0.321			
Baseline mitral insuff. stage III–IV	1.25	0.69–2.27	0.460			
Ischaemic aetiology	1.11	0.79–1.57	0.539			
ΔQRS < 10 ms	1.94	1.32–2.83	**0.001**	1.65	1.23–2.35	**0.015**
ΔQRS = 10–20 ms	1.06	0.74–1.50	0.760			
ΔQRS > 20 ms	0.59	0.41–0.85	**0.004**			
Atrial fibrillation	1.43	0.94–2.16	0.092			
Baseline NYHA III–IV	1.95	1.38–2.76	<**0.001**			
Non-LBBB ECG	2.58	1.35–4.55	<**0.001**	2.28	1.71–4.98	<**0.001**

Values in bold illustrate *P*-values with statistical significance.

and worsened. Long-term survival demonstrated not only significant differences between them, but the differences in median survival and hazard ratios were amplified as compared with those based solely on the echocardiographic response, especially in patients with the least favourable prognosis: the median survival was 39.7 months in echocardiographic progressors, as compared with 24.4 months in the worsened cohort.

Our results show both similarities and dissimilarities with the observations in recent publications which also applied the redefined classification of CRT response. In the pre-planned 5-year FU analysis of the REVERSE study both the CCS and the change in LV ESVi were used to classify patients as improved, stabilized and worsened.[14] In line with our findings, 5-year all-cause mortality rates in improved and in stabilized patients were better as compared with those in the worsened group based on either the CCS or on the reverse remodelling endpoints. However, unlike in our research, similar survival rates were demonstrated in improved and in stabilized patients. The same response categories were used in a pooled analysis of five prospective studies including more than 1600 patients.[7] Again, worsened patients had significantly lower survival as compared with those in the improved and in the stabilized groups stratified 6 months after CRT implantation according to the changes either in CCS or in LV ESVi. However, while outcomes were similar in improved and in stabilized patients based on the LV ESVi response, improved patients had significantly better survival than those in the stabilized group when classified by the changes in CCS. In our study, three markedly different survival curves were obtained using the combined method to assess the response to CRT based on the changes in both LVEF and on the presentation of any HHF or VA event within 12 months after CRT implantation. Of note, patients classified as worsened had strikingly low life expectations. Our classification scheme thereby seems appropriate to identify patients who require intense monitoring and urgent consideration of therapy escalation possibly including the use of an assist device or HTX. All three elements of the assessment we used are parts of the routine FU of CRT patients at any HF or arrhythmia clinic without the need for additional diagnostic effort in daily clinical practice.

Conclusions

A composite endpoint including the change in LVEF and the occurrence of HHF or sustained VA within 1-year post-implantation predicts long-term survival in patients after CRT-D implantation. Based on three distinct survival curves, improved, stabilized and worsened outcomes were demonstrated. The best survival rates (improved) were found in patients who showed an increase (>10%) or no change in LVEF and had no HHF or sustained VA event. The stabilized group included patients with echocardiographic signs of LV reverse remodelling who experienced a clinical event (HHF or sustained VA) and those with no change in LVEF and no clinical event. Worsened patients had at least 1 clinical event in addition to no change or a decline in LVEF. Median survival in stabilized patients was significantly better as compared with those in the worsened group with strikingly poor prognosis in the latter one. In addition to the echocardiographic signs of reverse LV remodelling, these results argue for the inclusion of clinical events to assess the early response to CRT to predict long-term outcome. In line with recent reports, our data also support the use of stabilized group as a distinct category.

Clinical implications

Our data demonstrated that in addition to pre-implantation parameters which are known predictors of the long-term outcome, the changes in echocardiographic parameters and the occurrence of clinical events during the 1st year post-implantation add valuable information to refine the prognosis and to select patients requiring intensified monitoring and therapy escalation.

Limitations

This is a single centre observational study involving HFrEF patients predominantly treated at a tertiary care academic centre, therefore this model should be validated in a prospective multicenter trial on a large number of patients receiving medical therapy according to contemporary guideline recommendations. Only CRT patients implanted with a CRT-D device capable of arrhythmia documentation were included. Echocardiographic information was mainly obtained via chart review, and the imaging studies could not be readjudicated. In order to minimize the potential distortion due to miscategorization of patients, an absolute increase of 10% in the LVEF was chosen as a cut off value for the CRT response, which was not unprecedented.[23–25] All-cause mortality was used as the only endpoint in our research without considering other clinically meaningful changes in symptoms, quality of life and functional status. SGLT2-inhibitors were not available in our country during the study period, and the administration of sacubitril/valsartan was low in the study population. These medications might have influenced the outcome of our patients.

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Conflict of Interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Distribution of HHF and VA episodes during the 1st year post-implantation in responder (left panel), non-progressor (middle panel) and progressor patients (right panel). White and blue sectors correspond to HHF or VA events, respectively, red sector depicts the occurrence of both HHF and VA events. (HHF = hospitalization for heart failure; VA = sustained ventricular arrhythmia).

Figure S2. The influence of the different types of clinical episodes on the long-term prognosis of the overall CRT-D population estimated by Kaplan–Meier survival analysis (A) and the corresponding *p*-values (B). The relationship between the numbers and types of the delivered ICD therapies (only ATP, only shock, both) within the 1st year post implantation and the long-term survival as demonstrated by Kaplan–Meier estimation (C) and the corresponding *p*-values (D). HHF = hospitalization for heart failure; VA = sustained ventricular arrhythmia, ATP: anti-tachycardia pacing).

Table S1. Heart failure treatment of echocardiographic responder, non-progressor and progressor patients prior to implantation.

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