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Patient-assessed short-term positive response to cardiac resynchronization therapy is an independent predictor of long-term mortality

Christian Reitan, Zoltan Bakos, Pyotr G Platonov, Carl-Johan Höijer, Johan Brandt, Lingwei Wang, Rasmus Borgquist

Arrythmia Clinic, Lund University, Skane University Hospital, Sweden

Skane University Hospital

Getingevägen

S-221 85 Lund

Sweden

Phone: +46 46 171000

Address for correspondence:

Rasmus Borgquist

Arrythmia Clinic, Lund University, Skane University Hospital, Sweden

rasmus.borgquist@med.lu.se

Phone: +46 46174281 or +46 704057350

Abstract

Introduction: Cardiac resynchronization Therapy (CRT) has a well-documented positive effect on mortality and heart failure morbidity. The aim of this study was to assess the long-term survival and the predictive value of self-assessed functional status on the long-term prognosis of patients treated with CRT-pacemaker (CRT-P).

METHODS: Data was retrospectively collected from medical records of 446 consecutive patients implanted with CRT-P at a large volume Swedish tertiary care centre. Primary outcome was all-cause mortality, predictive variables were assessed by log-rank test and univariate cox regression. 309 patients had reliable information available regarding early improvement after implantation and were included in the multivariate analyses.

Results: The cohort was followed for a median of 79 months and was similar in baseline characteristics compared to major controlled trials. During follow-up 204 patients died, yearly mortality was 11.7%. Early improvement of self-assessed functional status was a strong independent predictor of survival (HR 0.59 CI 0.40-0.87 p=0.007), together with well-known predictors; NYHA III-IV vs I-II (HR 1,66 CI 1.09-2.536 P=0.018), age (HR 1.05 CI 1.03-1.08 p<0.001), male gender (HR 2,0 CI 1.11-3,45 P=0.021) and loop diuretic use (HR 4,41 CI 1,08-18,02). Patients with early improvement of self-assessed functional status had better 2-year and 5 year survival (p<0.001).

Conclusions: Real-life patient characteristics and predictors of outcome compare well with those in published prospective trials. Self-assessed functional status is a strong predictor of long term survival, which may have implications for a more active follow-up of patients without spontaneous improvement.

Background

Cardiac Resynchronization Therapy (CRT) has a proven effect on morbidity and mortality in heart failure patients with wide QRS complex and reduced systolic left ventricular ejection fraction (LVEF)[1-3]. The initial studies enrolled patients with severe heart failure symptoms (NYHA class III and IV), but more recently similar beneficial effects have been shown on patients with mild to moderate heart failure symptoms (NYHA class I/II)[4-6].

CRT induces reverse remodeling of the dilated left ventricle, and there is some evidence that reverse remodeling in itself is associated with lower risk of ventricular arrhythmias, indicating that there should be a more favourable prognosis for "responders" as compared to "non-responders"[7, 8]. However, few studies have reported the patients' self-assessed opinion on the effect of CRT treatment, and to the best of our knowledge there are no published long-term follow-up cohorts in which the subjective response has been evaluated as a predictor for survival. Indeed, in the recently published update of European guidelines for CRT, it is speculated that "the link between benefits to symptoms and prognosis may not be strong"[9]. Furthermore, the term "responder" is quite unclear and is defined differently in the different major studies. The aim of this study was to investigate the long-term and very-long-term prognosis for patients with CRT-P treatment, and evaluate the added value of short-term early improvement of self-assessed functional status in relation to long-term prognosis. Secondary objectives were to investigate any gender differences in mortality and response rates.

Methods

Study Population and data collection

We retrospectively screened the medical records of all patients receiving CRT implants (CRT-D or CRT-P) from 1999 through 2012 at a large-volume tertiary care centre in Sweden. Skåne University hospital (SUS) is one of Sweden's largest hospitals, and the pacemaker department serves a population of 1,7 million people in the south of Sweden.

The hospital implanted its first CRT device in 1999 and it is responsible for the implantation of every such device in the entire region. All implants were tracked through the hospital records, making a comprehensive long-term follow-up possible. Procedures with non-successful left ventricular lead implant or immediate explant (within 2 months of implant, e.g. due to systemic infection) and patients aged less than 18 years at the time of implant were excluded from the analysis. The baseline evaluation was the standard clinical evaluation, i.e. echocardiography, ECG, anamnestic and physical examination. The first follow-up evaluation was carried out within 2 months post implant, and at this point the patients were asked if they had experienced an improvement in their functional status compared to pre-implant. Three possible answers were noted in the records; "Yes, definitely", "No, unchanged" or "No, it has worsened". Based on these responses the patients were divided into two groups; "definite responders", or "non-responders" (including non-responders with worsened condition and those with unchanged condition).

All patient baseline data were retrospectively gathered from individual assessment of medical records by the same individual and cross-validated with data from the Swedish Pacemaker Registry and the Swedish Death and Hospital Discharge Registries. The primary endpoint variable was death during follow-up, and secondary endpoint was death or hospitalisation for heart failure. The study was approved by the local ethics committee.

Statistical methods

Continuous or nominal data are presented as mean ± SD or as median [IQ range] as appropriate. Categorical data are presented as number and percentages. Differences in mean were evaluated with student's t-test and non-Gaussian distributed variables were tested with the Mann-Whitney U-test. Categorical variables were tested with Fisher's exact test or the Chi^2-test as appropriate.

A Kaplan-Meier plot was used to compare survival over time between groups, and univariate Cox regression analysis was performed to calculate possible predictors of survival during follow-up. Variables with p-values below 0,20 were then included into a multivariate Cox regression analysis with stepwise backward conditional elimination (highest p-value out) in order to identify predictors of mortality. A p-value of <0.05 was considered significant. The statistical analyses were performed using SPSS Statistics (release 21.0, IBM, Chicago, IL).

Results

A total of 477 patients who had an attempted CRT-P implant between 1999 and 2012 were identified (see figure 1). 22 patients were excluded because of unsuccessful LV lead implant, five patients were aged <18 years at time of implant and one patient had his device explanted <2 months after implantation. 3 patients were lost to follow-up. Of the remaining 446 patients, 309 had a clear statement in the medical records at 2 months follow-up regarding patient assessed response, and these were included in the final analyses (See figure 1). The median follow up time for the included patients was 82 months (interquartile range 52). Table 1 shows baseline characteristics, pharmacological treatment, ECG and echocardiographic parameters of the cohort, for all patients and then stratified into two groups according to self-assessed response to treatment.

Long term prognosis

During follow-up 204 patients died, of whom 93 (48%) died from heart failure, 36 (18%) from cardiac arrest and 23 (12%) from acute myocardial infarction, the remainder from other causes. Five-year mortality was overall 51% (40% vs. 58% for responders and non-responders respectively, p< 0.001) and two-year mortality was 23% (15% vs 31%, p<0.001). Yearly mortality was 11.7% overall. Univariate and multivariate predictors of survival are presented in Table 2. Independent predictors of survival were self-assessed improvement of physical condition, female gender, lower age, lower NYHA class (I-II vs III-IV). Higher EF and wider QRS complex were borderline significant. Patients with NYHA class IV symptoms had a low likelihood of experiencing an improvement of symptoms (32% vs. 56% in the entire cohort), and the 2- and 5-year survival was significantly lower for these patients (2-year mortality 52%, 5-year mortality 73%, p=0.002 compared to the rest of patients). Loop diuretic therapy was associated with a higher mortality. Mode of death was primarily heart failure, cardiac arrest or myocardial infarction, together accounting for 83 % of all deaths in the study population (see Table 3).

The impact of early self-assessed positive response

In survival analysis for the whole group, survival was significantly better for patients with an early subjective positive response - this effect starts early and seems to become stronger with time, since the curves on the Kaplan-Meier plot continue to diverge during the whole follow-up period (see Figure 2). Patients who showed early positive response did not differ to a great extent at baseline from those who did not (see Table 1); they had slightly less symptoms (lower NYHA class), wider QRS complex and received ACE-inhibitors or Angiotensin blockers to a higher extent. It is notable that among the subjective responders there seems to be a shift from death caused by heart failure towards death caused by cardiac arrest or myocardial infarction (heart failure mortality was 59% vs. 41% for responders (p=0.042). Other causes of death were evenly distributed across both groups. Patients who were considered "non-responders" at the initial follow-up were not treated in a standardized fashion, and no statistical analyses on interventions were possible for the purpose of this study. The most common intervention was AV optimization using the Ritter algorithm or the iterative method. VV-optimization was not routinely used, but if it was used it was based on the aortic velocity time integral (VTI) method. Further interventions regarding changes in medication, treatment of concomitant anaemia etcetera, have not been analysed for this study.

Gender differences

Overall survival was significantly better for women, and gender did qualify as an independent predictor for survival, with mortality HR 2.0 (CI 1.1-3.5) for men. However, when considering the predictive value of subjective positive response, the entire predictive effect seems to be conferred to the male patient group (see Figure 3a and 3b). For the female patients, there was no significant difference in survival, when comparing the groups with an early self-assessed positive response or not.

Discussion

Study population

In this study we present a large cohort with patients treated with CRT-P, and very long-term follow-up data with almost no patients lost to follow-up.

Our main findings show that short-term subjective response adds independent predictive value for long-term survival, on top of other established criteria for positive effect of CRT. Mortality was higher than in the CARE-HF study, which showed a 2-year mortality of 18.0% and a 5-year mortality of 32.2%[10], but the patients in our cohort were older, a larger proportion had ischemic cardiomyopathy and atrial fibrillation was very common. As guidelines over time have changed towards preferential use of CRT-D, most likely there is a bias in our real-life material towards using CRT-P in patients perceived to have a higher degree of comorbidities and older age, thus also introducing a negative bias on survival.

As the present cohort was selected not by trial criteria but rather from cardiac resynchronisation therapy demand according to contemporary guidelines in a large real-world population where all cases was referred to the same clinic, these findings are probably a good measure of the CRT response in a population. All patients were covered by Swedish state health insurance, which means a socioeconomic bias in means of referral is unlikely. The number of patients lost to follow-up was very low, and we believe the findings are generalizable and can be compared to other long-term follow-up studies, previously published.[11, 12]

As expected, advanced age and reduced EF preoperatively were independent predictors of increased mortality. Similarly we show that more pronounced symptoms (higher

NYHA class) preoperatively correlated with an increased mortality in the long-term in univariate analysis, with borderline significance in the multivariate model. There was a trend for a shorter duration of QRS complexes being associated with a higher mortality, a difference which is likely correlated to the probability of mechanical dyssynchrony being higher the wider the QRS is. It is reasonable, and in line with current guidelines[9], that there is a greater potential for clinical improvement in patients with wider QRS complexes preoperatively than in patients with shorter QRS duration.

Early self-assessed improvement of functional status

We show for the first time that the subjectively perceived symptomatic improvement at two months post implant is a powerful independent predictor of very long-term survival. The remodeling effect of CRT may start immediately after implant, but the full effect is usually not expected until six months postoperatively (the time interval most often used for echocardiographic evaluation of CRT response). Nevertheless, the evaluation of response in our study was made within two months post-implant, and the predictive value for long-term mortality was strong. Even though there were some differences in baseline variables between the responders and non-responders, the effect on survival was significant when adjusted for covariates, and appears to provide an added value for prediction of survival. Interestingly, the curves on the Kaplan-Meier plot continue to diverge during the whole follow-up period, indicating that the short-term benefits indeed transform into long-term reduction of heart failure disease progression. Mullens et al. proposed an algorithm for managing non-responders,[13] and showed that the group of non-responders where a specific correction or optimization of the therapy could be carried out had a better prognosis than those where no identifiable cause for non-response was found. Optimizing the therapy is equally important as including the right patients and finding these patients early, before disease progression, and has a high clinical value.[14-16] Furthermore, as Cleland et al. points out, the term “responder” is quite unclear and involves the patient’s subjective experience as well as objective measures.[17]

Packer has proposed a clinical composite evaluation score as an endpoint for CRT-response[18], but although intuitive and reproducible, the Packer clinical score is not routinely used as a tool in everyday clinical evaluation of CRT patients. Our evaluation shows that a single question may be just as accurate in identifying the patients with positive (or absent) effect of CRT. This makes evaluation very easy and reproducible, and the fact that the patients' short time subjective improvement correlates strongly with long-term mortality suggests that this method could be a useful clinical tool. It is well known that the placebo effect is significant in patients receiving expensive implants and surgical procedures, and our results are likely attenuated by this, since some of the "responders" may not have had an actual positive objective improvement of cardiac function on the heart. Nevertheless the results are highly significant, and seem to identify a group of patients with significantly worse prognosis, if they do not feel improved after 2 months.

Our study, being retrospective, was not constructed to answer if a non-responder could be converted to a responder and if that "conversion" would translate into at better long-term prognosis comparable to the spontaneous positive responders. Some of the non-responders would have been referred to an echo-based re-evaluation of the pacemaker-settings, but due to the retrospective nature of the study we were not able to recapitulate in detail the interventions made for non-responders in this cohort. Future prospective trials will have to clarify if interventions transform into better outcome, and we believe that our results have added information pointing towards the incremental value of such a prospective trial.

Gender differences

As a pre-specified analysis, we wanted to investigate gender differences in outcome in our cohort. Previous studies have shown conflicting results regarding gender differences in CRT effect, with some studies reporting better effect of CRT in women[19-21], while others have reported a neutral or negative effect[6, 12, 22]. Our findings add to the existing data and support the notion that women seem to benefit more from CRT therapy than men. However, the number of women in our cohort was small (76 in all), and conclusions regarding this subgroup should therefore be made with caution because of low statistical power. Nevertheless, gender differences in CRT treatment is an important issue and need to be assessed again in future prospective trials, since women are consistently underrepresented in CRT therapy in general and CRT-D therapy in particular.

Notably, the discriminatory value of an early self-assessed positive response seems to lie within the group of male patients only. Women had a trend for higher response-rate and better survival as shown, but the missing association between early response and long-term prognosis may imply that the positive effects come with a more gradual onset in women. This would mean that an ambiguous or unchanged status at two months is not as conclusive for female CRT recipients, and a further follow-up at six months post-implant may be warranted before the patient is designated to be a definite responder or non-responder. These findings need further validation and should be interpreted with caution, due to the relatively few female patients in this cohort.

Limitations

This study was retrospective and non-randomized with no suitable control group, which should be considered when interpreting the results. Furthermore, CRT guidelines have changed over time which affects the cohort of this study, but at the same makes the results more generalizable since it is a real-life heterogeneous group of patients. The cohort is large for a single centre study but still smaller than the major randomized trials, which needs to be accounted for when interpreting the results. Standardized follow-up echocardiography data are missing, and those data would have been interesting to compare with the patients' own evaluation of the positive effect of CRT.

Conclusions

Our study shows that long-term mortality for CRT-P treated patients in a consecutive cohort was significantly higher than in randomized trials, and that the majority of these patients still die from heart failure. Self-assessed improvement of functional status in the short term is a strong predictor of improved survival in the long term in CRT treatment, something that should be assessed (by a simple question) and be considered as important information when CRT patients are followed in the outpatient clinics. The optimal time for evaluation of response to CRT may be different for women compared to men, and women may have a longer time to "full effect" of the therapy. Future research should focus not only on inclusion criteria, but also on how to handle early non-responding patients, and efforts should be made to "convert" non-responders to responders by optimizing implant techniques and device programming.

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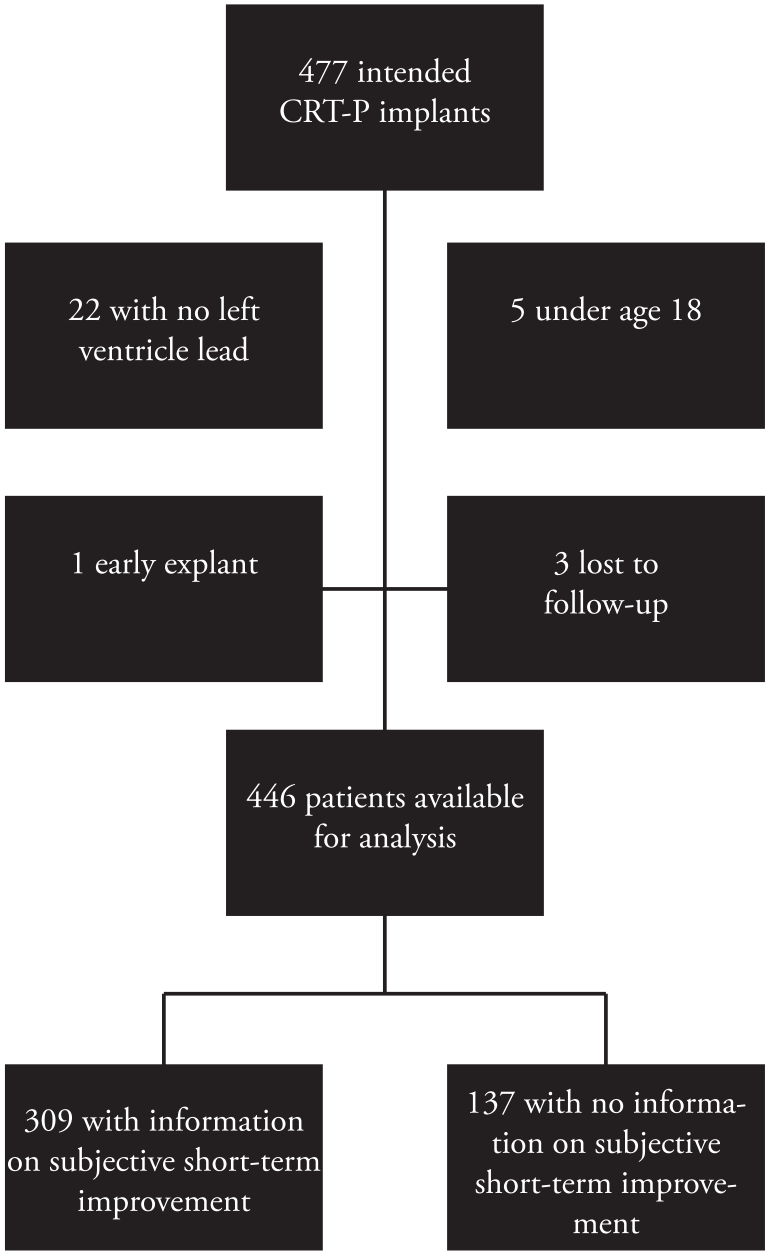
Tables and figures

Figure 1. flowchart, patient selection process.



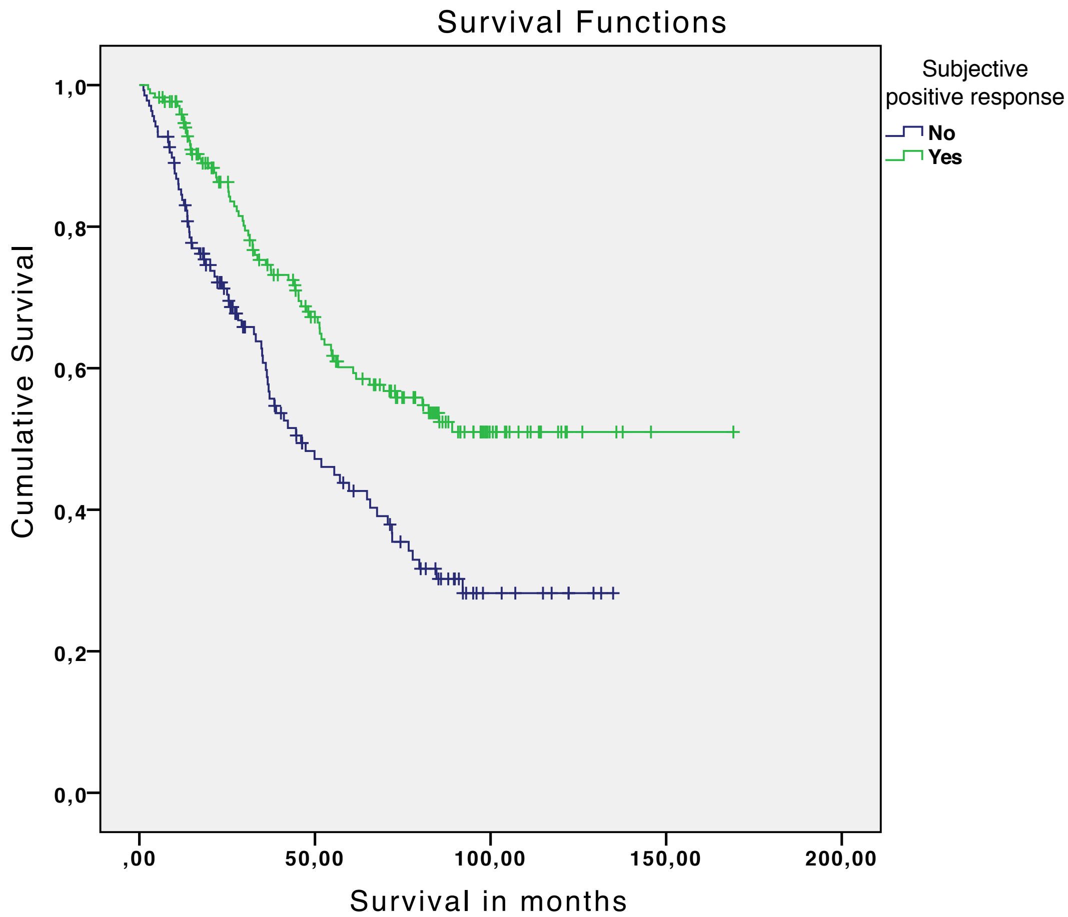
Subjective response	All CRTP n=446	No n=137	Yes n = 172	p-value
Male gender n=446 (%)	370 (83%)	115 (83,9%)	138 (80,2%)	0,458[1]
Age, years mean, (SD) n=446	72,1 (9,7)	72,5 (9,5)	70,7 (10,6)	0,136[3]
Ischaemic aetiology n=435	262 (60,2)	77 (58,3%)	106 (62,7%)	0,12
Dilated	127 (29,2)	35 (26,5%)	52 (30,8%)	
Other	43 (9,9%)	19 (14,4%)	10 (5,9%)	
NYHA Class n= 398				0,024[2]
Class I	4 (1%)	0 (0%)	2 (1,3%)	
Class II	54 (13,6%)	18 (14,4%)	18 (11,5%)	
Class III	304 (76,4%)	88 (70,4%)	128 (81,5%)	
Class IV	36 (9,0%)	19 (15,2%)	9 (5,7%)	
QRS Duration, ms (SD) n=438	169,9 (27,4)	165,5 (24,5)	172,9 (28,9)	0,019[3]
QRS duration > 150 ms	345 (77,4)	97 (70,8)	144 (83,7)	0,008[1]
Myocardial infarction n=446	249 (55,8%)	73 (53,3%)	101 (58,7%)	0,357[1]
Previous CABG, n=436 (%)	149 (34,2%)	48 (36,6%)	64 (37,4%)	0,905[1]
Previous angioplasty, n=318 (%)	76 (23,9%)	21 (22,1%)	27 (22,7%)	1[1]
Hypertension, n=446(%)	189 (42,4%)	60 (43,8%)	77 (44,8%)	0,908[1]
Diabetes, n=446 (%)	152 (34,1%)	52 (38,0%)	60 (34,9%)	0,634[1]
Haemoglobin mg/l (SD) n=188	130,5(16,6)	130,7 (16,0)	131,9 (16,7)	0,669[3]
Creatinine, g/dl (SD) n=213	124,2 (49,8)	121,5 (48,5)	122,0 (50,9)	0,946[3]
LV ejection fraction, n=428 [IQ]	25 (7)	25 (7)	25 (7)	0,712[4]
B-Blocker use, n=419 (%)	328 (78,3%)	101 (76,5%)	131 (78,9%)	0,674[1]
ACE-inhibitor or Angio-tensin-receptor blocker use, n=412 (%)	370 (89,8%)	112 (85,5%)	153 (93,3%)	0,033[1]
Aldosterone antagonist use, n=418(%)	231 (55,3%)	70 (53,4%)	94 (56,3%)	0,64[1]
Loop diuretic use, n=403 (%)	359 (89,1%)	109 (87,9%)	146 (90,1%)	0,57[1]
Class III antiarrhythmic use, n=421(%)	32 (7,6%)	6 (4,5%)	17 (10,2%)	0,082[1]

Digoxin use, n=399 (%)	118 (29,6%)	42 (35,3%)	52 (32,1%)	0,61[1]
Anticoagulant use, n=425 (%)	216 (50,8%)	71 (53,9%)	85 (50,9%)	0,642[1]
Block on ECG n=443 (%)				0,144[2]
LBBB	280 (63,2%)	80 (58,8%)	108 (62,8%)	
RBBB	9 (2,0%)	1 (0,7%)	6 (3,5%)	
Atypical	51 (11,5%)	23 (16,9%)	17 (9,9%)	
Paced	96 (21,7%)	31 (22,8%)	37 (21,5%)	
history of Atrial Fibrillation n=446	269 (60,3%)	86 (62,8%)	92 (53,5%)	0,106[1]
Previous pacemaker or ICD n=446	96 (21,5%)	31 (23,0%)	37 (22,0%)	0,89[1]
Median follow-up time n=446 [IQ]	79,0 (160,6)	82,5(59,3)	82,0 (47,7)	0,613[4]

Table 1. Baseline characteristics of the whole cohort and stratified for subjective response. 1 Fischers exact test, 2 Chi-square, 3 t-test, 4 Mann-Whitney

	Univariate			Multivariate		
Parameter	P-value	Hazard Ratio	CI	P-value	Hazard Ratio	CI
Male gender	0,033	1,566	1,038-2,364	0,021	1,995	1,107-3,452
Age, years mean	0,000	1,037	1,022-1,053	0,000	1,053	1,028-1,079
Ischaemic aetiology compared to dilated	0,001	1,728	1,259-2,372			
NYHA class III-IV/I-II	0,000	3,943	1,853-8,393	0,018	1,664	1,092-2,536
QRS Duration / 10 ms	0,154	0,964	0,917-1,014	0,105	0,941	0,874-1,013
Myocardial infarction	0,000	1,657	1,255-2,187			
Previous CABG	0,000	2,083	1,584-2,739			
Previous angioplasty	0,127	0,741	0,504-1,089			
Hypertension	0,711	0,950	0,722-1,249			
Diabetes	0,901	1,018	0,769-1,347			
LV ejection fraction, (%)	0,000	0,957	0,938-0,977	0,097	0,975	0,947-1,005
B-Blocker use	0,441	0,881	0,637-1,217			
ACE-inhibitor or ATII-blocker use	0,313	0,788	0,496-1,252			
Aldosterone antagonist use	0,007	1,485	1,117-1,975			
Loop diuretic use	0,000	4,640	2,059-10,456	0,039	4,406	1,077-18,018
Class I or III antiarrhythmic use	0,277	1,308	0,806-2,122			
Digoxin use	0,304	1,163	0,872-1,551			
Anticoagulant use	0,009	1,449	1,097-1,914			
Block on ECG other than LBBB	0,329	1,147	0,871-1,510			
Subjective improvement of condition	0,000	0,539	0,392-0,742	0,007	0,592	0,403-0,869
History of atrial Fibrillation	0,002	1,615	1,201-2,172			
Previous pacemaker or ICD	0,517	0,899	0,650-1,242			

Table 2. Univariate and multivariate Cox regression.

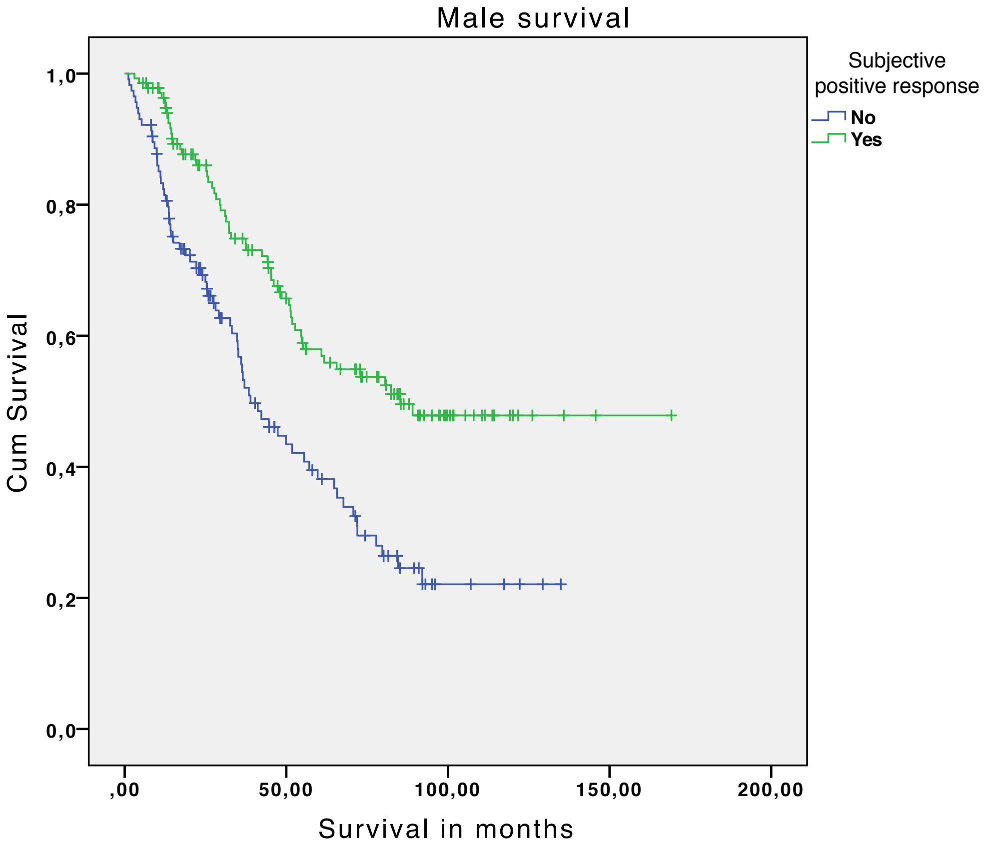


Months	Number exposed to risk
0	309
25	208
50	128
75	85
100	30
125	8

Figure 2. Kaplan-Meier curve showing survival for subjective responders and non-responders, respectively. p-value < 0,0001. Table showing idividuals exposed to risk.

			cause						
			AMI	Heart failure	Cardiac arrest	CVI	Malignancy	Renal failure	Other
Subjective response	No	Count	9	45	10	1	2	1	8
		% within no response	11,8%	59,2%	13,2%	1,3%	2,6%	1,3%	10,5%
	Yes	Count	11	26	14	1	4	0	7
		% within response	17,5%	41,3%	22,2%	1,6%	6,3%	0,0%	11,2%
Total		Count	20	71	24	2	6	1	15
		% within all	14,4%	51,1%	17,3%	1,4%	4,3%	,7%	10,8%

Table 3. Causes of death in the respective groups. n = 139



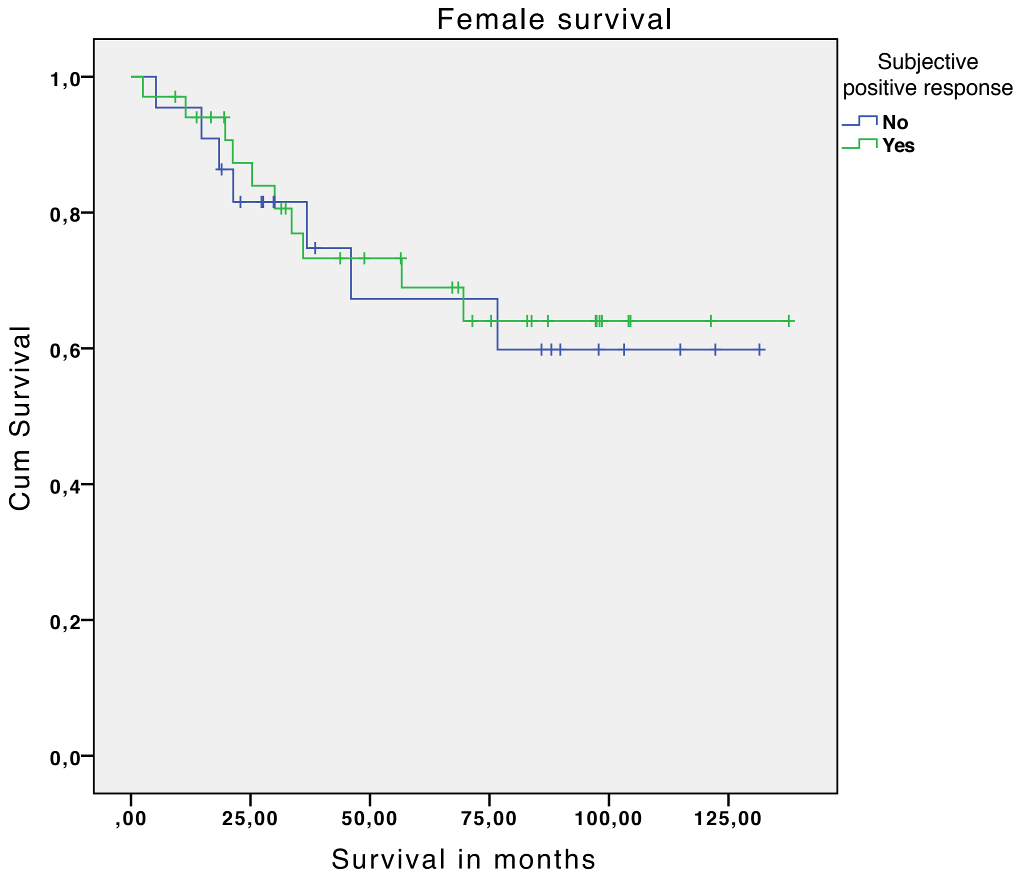


Figure 3. Kaplan-Meier curve showing survival for the male and female populaion. p-values; <0,001 and 0,825, respectively.