Long-Term Results of Cardiac Resynchronization Therapy: A Comparison between CRT-Pacemakers versus Primary Prophylactic CRT-Defibrillators

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Background: *Cardiac resynchronization therapy (CRT) with or without a defibrillator has a positive effect on mortality and morbidity for patients with heart failure. However, comparisons between CRT-defibrillators (CRT-D) and CRT-pacemakers (CRT-P) are relatively scarce outside the clinical trial setting. This study aimed to assess baseline characteristics in relation to long-term prognosis in patients treated with CRT, and to investigate the potential benefit of CRT-D versus CRT-P.*

Methods: *Data were retrospectively collected from the medical records of all consecutive patients treated with CRT-P or primary prophylactic CRT-D at a large tertiary care center between 1999 and 2012. Predictors of mortality were investigated, and time-dependent analysis was performed with all-cause mortality as the primary end point.*

Results: *A total of 705 patients were included (69.6 ± 10 years, 78% New York Heart Association classes III–IV, left ventricular ejection fraction median 25%, 16% female, 36% CRT-D). The patients were followed for a median of 59 months. Annual mortality differed between CRT-D primary prophylactic and CRT-P groups (5.3% and 11.8%, respectively), but when adjusted for covariates, CRT-D treatment (compared to CRT-P) was not associated with better long-term survival. Independent predictors of survival were: age, use of loop diuretics, hemoglobin levels, and use of renin angiotensin aldosterone system blockers.*

Conclusions: *In CRT treatment outside of the clinical trial setting, CRT-D treatment was not an independent predictor of long-term survival. Future research should focus on correct selection of the patients who receive enough benefit of an added defibrillator to justify CRT-D implantation instead of CRT-P treatment only. (PACE 2015; 38:758–767)*

cardiac resynchronization therapy, implantable defibrillator, long-term follow-up, heart failure, prognostic factors

Introduction

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] CRT induces reverse remodeling of the left ventricle, resulting in an increased ejection fraction and an improvement of heart failure symptoms. The initial studies enrolled patients with severe heart failure symptoms (New York Heart Association [NYHA] classes III and IV), but more recently similar beneficial effects have been shown on patients with mild to moderate heart failure symptoms (NYHA classes I/II).[4–7] Since the introduction of CRT in the late 1990s, the guidelines have evolved. The COMPANION study[3] showed an added mortality benefit of primary prophylactic CRT-defibrillators (CRT-D) as compared to CRT-pacemaker (CRT-P) and the use of CRT-D has increased greatly since then, in line with previous and current guidelines.[8–10] However, adding a defibrillator function increases cost and may have negative consequences for the patients' quality of life. The evidence for CRT-D treatment on a large scale is still debated and some researchers advocate more CRT-P implants.[11] If the reduction in cardiac mortality is substantial by left ventricular resynchronization only, it may not be justifiable to use CRT-D as a standard therapy, and perhaps this treatment should then be given

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only to those subgroups that derive significant benefit from it.

The larger published trials all show a large predominance of male patients with percentages ranging from 67% to 83% for the male group.[1,3,5,6,12] This stands in contrast to findings that suggest that women may in fact have greater benefit from CRT treatment than men,[5] and further gender-stratified analyses are advocated for in the literature. The aim of this study was to investigate the long-term prognosis for CRT-treated patients, and to identify independent predictors of long-time survival. Prespecified subanalyses included gender differences and a comparison between CRT-P and primary prophylactic CRT-D.

Methods

Study Population and Data Collection

We retrospectively included all consecutive patients receiving CRT implants (CRT-D or CRT-P) from 1999 through 2012 at a tertiary referral university hospital with a primary uptake area of approximately 1.7 million people. Patients with nonsuccessful 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, as were patients with secondary prophylactic implantable cardioverter defibrillator (ICD) indication. The baseline evaluation was the standard clinical evaluation, that is, echocardiography, electrocardiogram (ECG), blood sampling, anamnestic, and physical examination performed at primary, secondary, or tertiary care units. Qualification for CRT was evaluated at the operating unit in accordance with current guidelines at the time (which have changed during the inclusion period.[13–16] Tables with baseline characteristics are presented stratified by means of CRT-P or CRT-D treatment (Table I).

All patient baseline data were retrospectively gathered from manual assessment of medical records by the same individual (CR), cross-checked by an experienced electrophysiologist (RB), and cross-validated with data from the official Swedish pacemaker Registry and the Swedish Death and Hospitalization Registry from the National board of Health and Welfare. Comorbidities, laboratory results and imaging data were acquired. Atrial fibrillation was classified as paroxysmal or chronic, but for analyses both forms of atrial fibrillation were grouped together to create a dichotomous variable. The primary end point variable was death during follow-up. Routine follow-up of CRT patients included yearly device integrity checks and diagnostic interrogation. Devices were routinely programmed with standard fixed atrio-ventricular (AV) delays and echocardiography-based optimization (Ritter for AV delay and velocity time integral-method for ventriculo-ventricular [VV] delay), or in some cases according to recommendation from the Quickopt™ algorithm (in devices from St. Jude Medical [St. Paul, MN, USA] with this feature enabled). For nonresponders, an additional echocardiography-based AV- and VV-optimization was in most cases performed after the 2-month postoperative device follow-up.

Definitions

Ischemic etiology was defined as heart failure after major ischemic event (acute coronary syndrome with or without intervention, i.e., coronary artery bypass grafting or percutaneous coronary intervention treatment). Presence of hypertension, diabetes, and history of myocardial infarction was defined by medical records of treatment in combination with ICD-10 codes for these conditions.

Statistical Methods

Continuous variables are presented as mean ± standard deviation or as median (interquartile range [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 χ^2 test, or with Kruskal-Wallis analysis of variance for variables with multiple groups.

Kaplan-Meier plots were used to compare unadjusted survival over time between groups and univariate Cox regression analysis was performed to calculate possible predictors of survival during follow-up. Variables with high internal correlations (>0.3) were assessed manually, and the most clinically relevant variable was kept in the model. Variables with P values ≤ 0.20 were then included into a multivariate Cox regression analysis in order to identify predictors of mortality (Table II). A P value of < 0.05 was considered significant. The statistical analyses were performed using SPSS Statistics (release 21.0, IBM Corp., Armonk, NY, USA).

Results

Baseline Clinical Characteristics

A total of 811 patients who had a CRT implant between 1999 and 2012 were identified (see Fig. 1). Six patients were aged <18 years at time of implant. One patient had his device explanted <2 months after implantation, five patients were excluded due to unconventional CRT-indication

Table I.

Baseline Characteristics

Parameter	All (n = 705)	CRT-P (n = 448)	CRT-D (n = 257)	P Value
Male gender, n = 705 (%)	589 (83.5%)	372 (83%)	217 (84.4%)	0.674
Age (years), mean (SD), n = 705	69.6 (10.3)	72.1 (9.7)	65.3 (9.8)	<0.001
Ischemic etiology, n = 693	394 (56.9%)	262 (60.0%)	132 (51.6%)	0.004
Dilated	235 (33.9%)	129 (29.5%)	106 (41.4%)	
Other	60 (10.8%)	43 (9.8%)	17 (6.6%)	
NYHA class, n = 650				
Class I	15 (2.3%)	4 (1.0%)	11 (4.4%)	<0.001
Class II	131 (20.1%)	54 (13.5%)	77 (30.7%)	
Class III	453 (69.6%)	306 (76.5%)	147 (58.6%)	
Class IV	52 (8.0%)	36 (9.0%)	16 (6.4%)	
QRS duration (ms), (SD) n = 696	168 (27.9)	170 (27.9)	164 (27.5)	0.003
Myocardial infarction, n = 705	379 (53.8%)	250 (55.8%)	129 (50.2%)	0.158
Previous CABG, n = 687 (%)	212 (30.9%)	149 (34.0%)	63 (25.3%)	0.02
Previous angioplasty, n = 532 (%)	131 (24.6%)	76 (23.8%)	55 (25.9%)	0.608
Hypertension, n = 705 (%)	326 (46.2%)	189 (42.2%)	137 (53.3%)	0.005
Diabetes, n = 705 (%)	224 (31.8%)	153 (34.2%)	71 (27.6%)	0.078
LV ejection fraction, n = 771 (IQ)	25 (7)	25 (7)	25(7)	0.712
β-Blocker use, n = 684 (%)	565 (82.6%)	336 (78.7%)	229 (89.1%)	0.001
ACE inhibitor or angiotensin receptor blocker use, n = 661 (%)	602 (91.1%)	372 (89.9%)	230 (93.1%)	0.162
Loop diuretic use, n = 628 (%)	548 (87.3%)	361 (89.1%)	187 (83.9%)	0.062
Class I or III antiarrhythmic use, n = 671 (%)	46 (6.9%)	32 (7.6%)	14 (5.6%)	0.429
Digoxin use, n = 611 (%)	172 (28.2%)	120 (30.0%)	52 (24.6%)	0.185
Anticoagulant use, n = 675 (%)	344 (51.0%)	218 (51.1%)	126 (50.8)	1.0
ECG morphology, n = 701 (%)				0.008
LBBB	459 (65.5%)	280 (62.9%)	179 (69.9%)	
RBBB	20 (2.9%)	9 (2.0%)	11 (4.3%)	
Atypical	82 (11.7%)	51 (11.5%)	31 (12.1%)	
Paced	128 (18.3%)	98 (22.0%)	30 (11.7%)	
History of atrial fibrillation, n = 702	331 (47.1%)	223 (50.0%)	108 (42.2%)	0.05
Median follow-up duration (months), n = 705	58.9 (161.3)	79.1 (160.6)	26.7 (25.2)	<0.001
Creatinine, n = 476 (umol/L) (SD)	117.8 (62.2)	124.3 (47.9)	110.6 (74.5)	0.016
Hemoglobin (g/dL), n = 448 (SD)	13.3 (1.6)	13.16 (1.6)	13.5 (1.5)	0.014

Clinical data stratified by type of CRT device (CRT-P/CRT-D).
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; class I or III antiarrhythmic use = Vaughan-Williams classification; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ECG = electrocardiogram; LBBB = left bundle branch block; LV = left ventricular; NYHA = New York Heart Association; RBBB = right bundle branch block; SD = standard deviation.

(nonheart failure), and three patients were lost to follow-up, with no information on survival in the Cause of Death registry. Ninety-one patients had received CRT-D as secondary prevention and were excluded from analyses. Out of the 705 cases available for analysis, 448 (64%) were CRT-P-patients and 257 (36%) were patients with primary prophylactic CRT-D. The median follow-up time was 59 (4–165) months. Table I shows baseline characteristics, pharmacological treatment, ECG, and echocardiographic parameters of the cohort, stratified according to type of device implanted. Compared to patients with CRT-D, the CRT-P-treated patients were older, more symptomatic (higher NYHA class), had higher creatinine and lower hemoglobin levels, and had a higher incidence of ischemic etiology. The patients in the CRT-D group were to a higher extent treated with β-blockers and were more likely to have hypertension.

Mortality

Yearly mortality was overall 10.05/100 patient years; 5.3 in the primary prophylactic

Table II.

Predictors of Mortality

Parameter	n = 705	Univariate Analysis			Multivariate Analysis		
		P Value	Hazard Ratio	CI	P Value	Hazard Ratio	CI
Male versus female gender	705	0.172	1.292	0.895–1.865	0.681	1.140	0.610–2.130
Age, years	705	**<0.001**	1.045	1.030–1.060	**0.024**	1.032	1.004–1.060
Ischemic etiology compared to other	629	**<0.001**	1.856	1.386–2.486	0.857	1.046	0.642–1.702
NYHA class I–II versus III–IV (ref)	651	**<0.001**	0.286	0.163–0.501	0.121	0.547	0.255–1.172
QRS duration/10 ms	696	0.993	1.000	0.956–1.047			
QRS duration greater than 150 ms	696	0.083	0.769	0.572–1.035	0.065	0.636	0.393–1.028
Myocardial infarction	705	<0.001	1.764	1.357–2.294			
Previous CABG	687	<0.001	2.099	1.620–2.719			
Previous angioplasty	532	0.395	1.175	0.810–1.703			
Hypertension	705	0.061	1.289	0.988–1.681	0.328	0.796	0.504–1.257
Diabetes	705	0.338	1.138	0.874–1.482			
LV ejection fraction (%)	685	**<.001**	0.956	0.938–0.975	**0.006**	0.952	0.919–0.986
β-Blocker use	684	0.106	0.774	0.567–1.056	0.647	0.879	0.505–1.530
ACE inhibitor or angiotensin receptor blocker use	661	**0.032**	0.628	0.411–0.960	**0.030**	0.475	0.243–0.929
Loop diuretic use	628	**<0.001**	4.567	2.152–9.694	**0.038**	3.494	1.074–11.371
Class I or III antiarrhythmic use	671	0.184	1.356	0.866–2.124	0.156	0.590	0.285–1.223
Digoxin use	611	0.317	1.149	0.875–1.510			
Anticoagulant use	675	**0.019**	1.370	1.054–1.780	0.368	0.786	0.465–1.328
ECG other than LBBB	689	**0.004**	1.466	1.131–1.899	0.192	1.416	0.840–2.389
History of atrial fibrillation	702	**<0.001**	1.691	1.308–2.186	0.235	1.362	0.818–2.269
Previous pacemaker or ICD	689	0.182	1.233	0.907–1.677	0.678	0.855	0.408–1.791
CRT-D versus CRT-P	705	**<0.001**	0.416	0.289–.600	0.103	0.643	0.378–1.094
Creatinine preimplant	476	**<0.001**	1.003	1.002–1.005	0.407	1.002	0.998–1.005
Hb preimplant (g/dL)	448	**0.004**	0.847	0.757–0.947	**0.037**	0.854	0.736–0.990

Time-dependent analysis of hazard ratio for mortality (Cox regression analysis).
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; CI = confidence interval; class I or III antiarrhythmic use = Vaughan-Williams classification; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LV = left ventricular; NYHA = New York Heart Association; Ref = reference category.
$P < 0.05$.

CRT-D group and 11.8 in the CRT-P group (Fig. 2). Unadjusted crude mortality rate was significantly lower in the primary prophylactic defibrillator group as compared to pacemaker only group (HR 0.416, confidence interval [CI] 0.289–0.600, P < 0.001). Univariate and independent predictors of mortality for the whole cohort are presented in Table II. CRT-D was a strong univariate predictor of increased survival, but when corrected for cofactors in the multivariate model, the effect was only a trend toward increased survival with a hazard ratio (HR) of 0.643 as compared to CRT-P (P = 0.103). Independent predictors of survival were age (HR 1.032, P = 0.024), LVEF (HR 0.952, P = .006), angiotensin-converting enzyme inhibitor use (HR 0.475, P = 0.030), loop diuretic use (HR 3.494, P = 0.038), and blood hemoglobin concentration preimplant (HR 0.854, P = 0.037). Five-year survival was 65.7% for CRT-D and 49.0% for CRT-P (P = 0.074). Two-year survival was significantly higher in the CRT-D group (85.0% vs 75.8% in the CRT-P group, P = 0.021).

Gender Differences

Women were much fewer than men (n = 116 vs 589) in the cohort. The only baseline difference between the groups was that men were more likely to have ischemic heart disease and to have a history of acute myocardial infarction, coronary artery bypass graft operation, and percutaneous coronary intervention, all with P values <0.001. When stratifying for gender

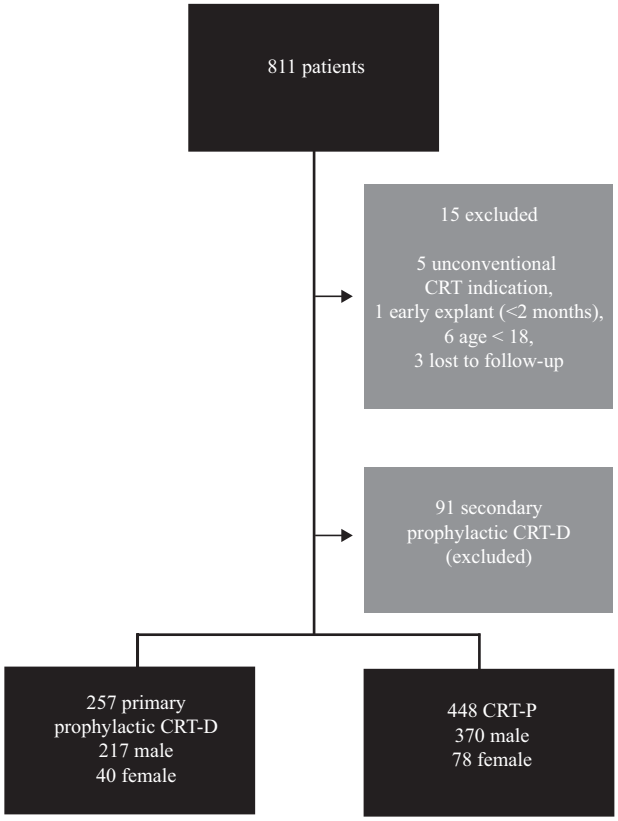


Figure 1. *Patient selection process. Flowchart over patients included in the study. CRT = cardiac resynchronization therapy; CRT-D = CRT with defibrillator*

and CRT-P or CRT-D, the Kaplan-Meier plots showed a significantly better survival for women in the CRT-P group (P = .029), and men selected for CRT-P had a particularly high mortality (see Figs. 3A and B). Mortality for women was overall 8.1/100 patient years, lowest for CRT-P,[7,9] for CRT-D primary prophylactic 8.8%. In a separate multivariate cox regression for CRT-P patients only, women had a significantly better long-term survival than men (HR 0.64, 95% CI 0.42–0.96, P = 0.03).

Discussion

CRT-D Treatment Compared to CRT-P Treatment

We present a comprehensive long-term follow-up of consecutive CRT-treated patients in a large real-life cohort. The results did not show that CRT-D was an independent predictor of survival even though there was a trend toward it. Although 2-year survival is better for patients with CRT-D compared to those with CRT-P, 5-year survival does not differ significantly. Patients with CRT-P have significantly more comorbidities than those with CRT-D, and with retrospective data any direct comparison must therefore be interpreted with caution. Nevertheless, it is notable that the added value of CRT-D was not strong enough to qualify as an independent predictor of long-term mortality, a finding that may indicate that the most significant part of the mortality benefit in this population is from the CRT-treatment and not the defibrillator treatment.

It is possible that successful CRT in itself, with reverse remodeling and lower filling pressures, is able to reduce the incidence of ventricular arrhythmias and increase ejection fraction and in effect obviate the need for an added defibrillator in many CRT-treated patients.[12,17] This is supported by the results from the extension study of CARE-HF (CArdiac REsynchronization in Heart Failure), in which there was a significant reduction in sudden cardiac death for CRT-P-treated patients.[18] If the reduction in cardiac mortality is substantial by left ventricular resynchronization only, it may not be justifiable to use CRT-D as a standard therapy, and perhaps this treatment should then be given only to those subgroups that derive significant benefit from it. Other follow-up studies have nevertheless indicated a benefit for CRT-D as compared to CRT-P, regardless of etiology of heart failure,[19,20] in line with the previously published randomized trials.[3,6] In a recent study by Kutyifa et al., a mortality benefit was seen for CRT-D in patients with ischemic cardiomyopathy but not for patients with dilated cardiomyopathy.[21] However, patients included in randomized trials tend to be healthier and better cared-for compared to patients in registries outside the trials, and the diverging results need to be addressed since most patients who receive CRT treatment in fact do so without being included in any clinical trial. Number needed to treat and total added cost for CRT-D is highly relevant, and these figures should ideally be based on multiple sources of reliable "real-world" data. The initial device cost of a CRT-D is higher than that of a CRT-P, there is a risk of potentially harmful inadequate or unnecessary shocks, and in order to justify primary prophylactic CRT-D treatment from a health-economic perspective, one would like to see a mortality benefit in the long term as well as in the short term. CRT-D treatment was not an independent predictor of survival, even though the cohort was fairly large. This could of course suggest that the study was underpowered or that the criteria for CRT-D treatment should be refined, especially considering the added costs and risks of complications with this type of treatment. Narrowing down inclusion criteria and identifying subgroups with a high benefit from CRT-D treatment would be beneficial, and our findings support the ongoing debate which advocates for a more widespread use of CRT-P

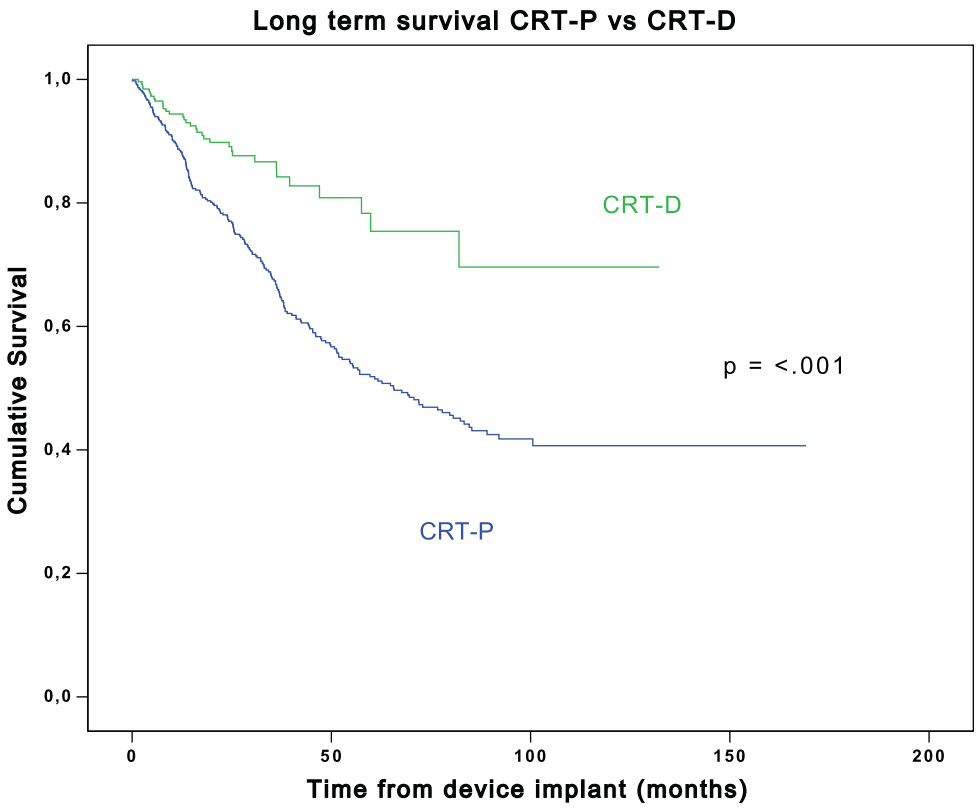


Figure 2. *Long-term survival for patients with CRT treatment. Kaplan-Meier curves showing survival for patients with cardiac resynchronization therapy (CRT) treatment, stratified for pacemaker (CRT-P) or defibrillator (CRT-D).*

instead of just routinely supplying all patients with a CRT-D.[11]

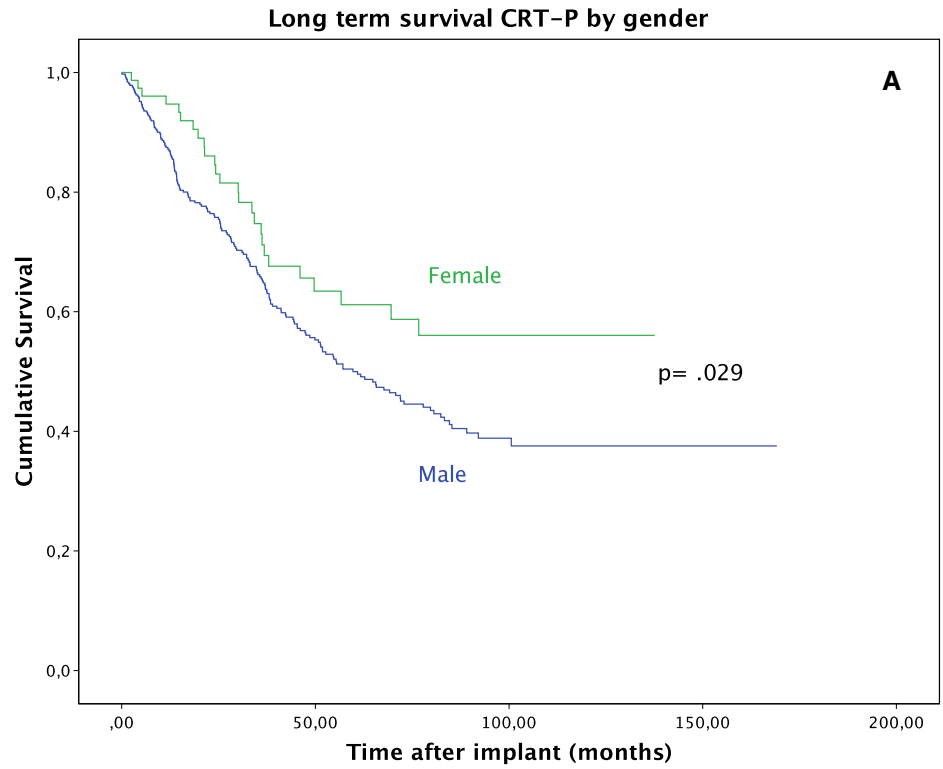
Independent Predictors of Long-Term Survival

The patients in our study compare well with those of the previously published studies; the only notable differences were that our cohort was slightly older than in the randomized trials, and that more patients were male and had a history of atrial fibrillation (Table III). A higher hemoglobin concentration and use of renin angiotensin aldosterone system blockers independently predicted long term survival. Use of loop diuretics and a recorded history of atrial fibrillation were associated with higher mortality.

Some well-known criteria did not qualify as independent predictors of mortality in this cohort, most notably diabetes mellitus and impaired renal function as estimated by S-creatinine values. Diabetes was common, 32% of all patients had this condition, and perhaps the high prevalence of diabetes and the overall high mortality in heart failure in this cohort obscured the expected increased mortality for diabetic patients. S-creatinine was a strong predictor in univariate analyses but did not show an independent predictive value, most likely due to presence of multiple other comorbidities in patients with renal failure. QRS duration was not an independent predictor, but there was a trend for better survival for patients with baseline QRS duration >150 ms (HR 0.636, P = 0.065, CI 0.393–1.028).

Gender Differences

In our study, as well as in many other studies, the number of women who received CRT was much lower than the number of men even though their benefit from CRT may be comparable or superior to men's.[22,23] For our entire cohort, survival also looked better for women (see Fig. 3), but when correcting for covariables gender was clearly not an independent predictor of survival, implying instead that the women selected for CRT had fewer comorbidities than men. This finding also raises the question whether women with more comorbidity (i.e., comparable to the group of men with CRT) are in fact not referred for CRT treatment to the same extent as men with similar high comorbidity. In the subgroup of CRT-P treated patients, mortality was clearly lower



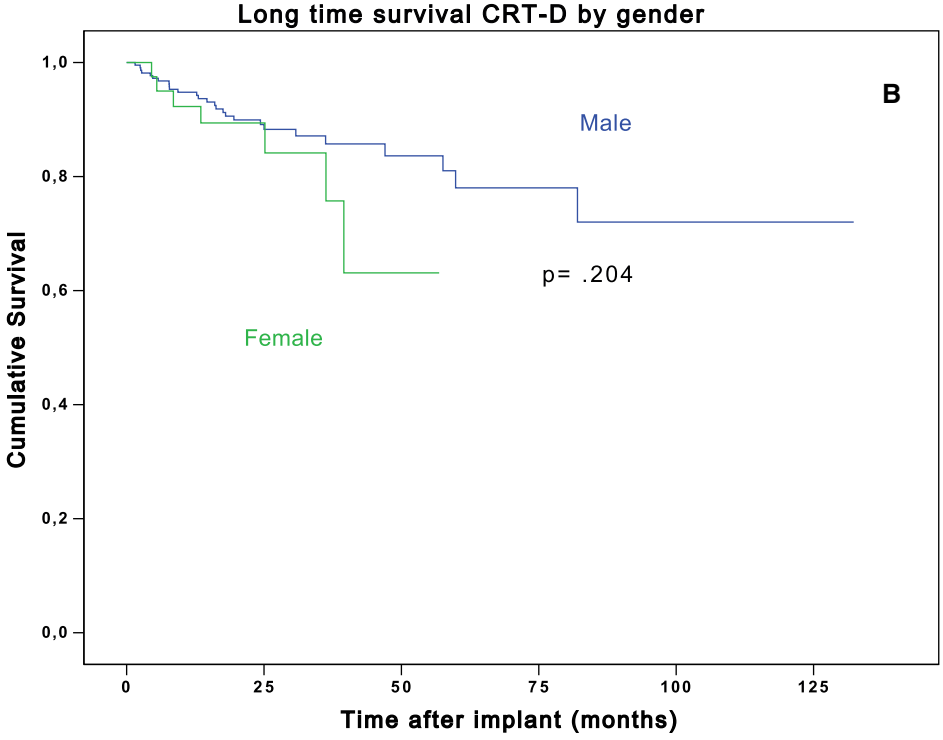


Figure 3. *Long-term survival for men and women with CRT treatment. Kaplan-Meier curves showing survival for patients with CRT-P treatment (panel A) and CRT-D treatment (panel B), stratified for gender. Abbreviations as in previous figures.*

Table III.

Study Comparison

Study (Year)	Study Characteristics (No. of Patients)	Mean Follow-Up (Months)	Age, Years, Mean (%)	Male (%)	Ischemic Cardiomyopathy (%)	Mean Ejection Fraction (%)	QRS Duration m(s)	NYHA Class (%)	AF (%)	LBBB (%)	Yearly Mortality for CRT-Treated Patients
COMPANION(3) (2004)	CRT-D/CRT-P/OMT (595/617/308)	14.8–16.5	67	67	55	22	160	III/IV: 100	NR	73	15% (CRT-P) 12% (CRT-D)
CARE-HF(1) (2002)	CRT/OMT (409/404)	29.4	66	74	38	25	160	III/IV: 100	0	NR	7.9% (after 37 months—the extension study)
REVERSE(12) (2008)	CRT-D/ICD (419/191)	12	62 (11)	79	55	27 ± 7	153 (12)	I/II: 100	0	NR	1% (after 24 months, European cohort)
MADIT-CRT (5)(2009)	CRT-D/ICD (1089/731)	28.8	65 (11)	75	55	24 ± 5	65% > 150	I/II: 100	12	70	2.8%
RAFT(6) (2010)	CRT-D/ICD (894/904)	40	66 (9)	83	67	23 ± 5	158 (24)	I/II: 80, III/IV:20	13	73	6.2%
Morani et al.(20) (2013)	CRT-P/CRT-D (108/266)	Median 55	69 (10)	80	56	27 ± 5	168 (31)	II: 24, III: 62, IV: 14	NR	NR	6.6% (CRT-D) 10.4% (CRT-D)
Bai et al.(19) (2005)	CRT-P/CRT-D (147/395)	27 (18)	66/67 (CRT-D/CRT-P)	77	66	19.92 ± 7.67/ 19.99 ± 8.09	160.52 ± 24.48/ 164.38 ± 23.82	III: 81/79, IV:19/21	NR	NR	8.3% (CRT-D)
Reitan et al. (2014)	CRT-P/CRT-D (257/448)	59	70 [10]	84	57	25 [7]	168 (±28)	I/II: 22, III/IV: 78	47	66	5.3% (CRT-D primary) 11.8% CRT-P

Comparison with previous studies regarding baseline characteristics and yearly mortality.
AF = atrial fibrillation; CRT-D = cardiac resynchronization therapy with defibrillator, CRT-P = cardiac resynchronization with pacemaker; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; NYHA = New York Heart Association; OMT = optimal medical therapy.

for women than for men, supporting previous evidence that women have a better effect *per se* of resynchronization than men do.[23,24] The number of female patients in our cohort was low, and these gender-based trends must therefore be interpreted with caution, and importantly, there were no data to investigate the number of women in the population that qualified for treatment compared to men. However, the difference in crude numbers is large, and could imply underutilization of CRT for women.

Limitations

The results must be interpreted in the light of the study design and that the patients were recruited from a single high-volume institution. Since the study was retrospective, there was no formal power calculation prior to the analyses, and one should be aware of the fact that lack of statistical significance in such a case does not prove equality between the studied groups. There was no non-CRT control group, which precludes direct evaluation of the benefit of CRT treatment compared to optimal medical treatment. Patient characteristics differed between the CRT-P and CRT-D groups and although the statistical analyses were adjusted for this, there may still be residual "nonmeasureable" differences in patient characteristics that were not accounted for.

Although it is a large single-center study, we cannot exclude a referral bias even though the cohort should represent all implanted patients in the geographical region. There is also the possibility of nonrandom distribution of missing variables.

Conclusions

Real-life preimplant patient characteristics and predictors of long-time survival in CRT-treated patients compare well with those in the published prospective trials. After multivariable analysis, CRT-D treatment was not associated with improved survival. Future research should focus on optimal identification of the patients who are likely to receive enough benefit of an added defibrillator to justify the risk of defibrillator-related side effects and the increased cost for the health care system, as compared to CRT-P treatment only.

References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346:1845–1853.
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352:1539–1549.
3. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350:2140–2150.
4. St John Sutton M, Ghio S, Plappert T, Tavazzi L, Scelsi L, Daubert C, Abraham WT, et al. Cardiac resynchronization induces major structural and functional reverse remodeling in patients with New York Heart Association class I/II heart failure. Circulation 2009; 120:1858–1865.
5. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009; 361:1329–1338.
6. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010; 363:2385–2395.
7. Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, Daubert JP, et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med 2014; 370:1694–1701.
8. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2013; 127:e283–e352.
9. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008; 29:2388–2442.
10. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:1977–2016.
11. Daubert JC, Donal E, Linde C. A plea for the wider use of CRT-P in candidates for cardiac resynchronisation therapy. Heart Fail Rev 2012; 17:767–775.
12. Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, Szili-Torok T, et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: Insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. J Am Coll Cardiol 2009; 54:1837–1846.
13. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013; 34:2281–2329.
14. Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, Ponikowski P, et al. 2010 focused update of ESC guidelines on device therapy in heart failure: An update of the 2008 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Eur Heart J 2010; 31:2677–2687.
15. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008; 29:2388–2442.

16. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33:1787–1847.
17. Di Biase L, Gasparini M, Lunati M, Santini M, Landolina M, Boriani G, Curnis A, et al. Antiarrhythmic effect of reverse ventricular remodeling induced by cardiac resynchronization therapy: The InSync ICD (Implantable Cardioverter-Defibrillator) Italian Registry. J Am Coll Cardiol 2008; 52:1442–1449.
18. Cleland JG, Freemantle N, Erdmann E, Gras D, Kappenberger L, Tavazzi L, Daubert JC. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. Eur J Heart Fail 2012; 14:628–634.
19. Bai R, Di Biase L, Elayi C, Ching CK, Barrett C, Philipps K, Lim P, et al. Mortality of heart failure patients after cardiac resynchronization therapy: Identification of predictors. J Cardiovasc Electrophysiol 2008; 19:1259–1265.
20. Morani G, Gasparini M, Zanon F, Casali E, Spotti A, Reggiani A, Bertaglia E, et al. Cardiac resynchronization therapy-defibrillator improves long-term survival compared with cardiac resynchronization therapy-pacemaker in patients with a class IA indication for cardiac resynchronization therapy: Data from the Contak Italian Registry. Europace 2013; 15:1273–1279.
21. Kutyifa V, Geller L, Bogyi P, Zima E, Aktas MK, Ozcan EE, Becker D, et al. Effect of cardiac resynchronization therapy with implantable cardioverter defibrillator versus cardiac resynchronization therapy with pacemaker on mortality in heart failure patients: Results of a high-volume, single-centre experience. Eur J Heart Fail 2014; 16:1323–1330.
22. Yarnoz MJ, Curtis AB. Sex-based differences in cardiac resynchronization therapy and implantable cardioverter defibrillator therapies: Effectiveness and use. Cardiol Rev 2006; 14:292–298.
23. Zabarovskaja S, Gadler F, Braunschweig F, Stahlberg M, Hornsten J, Linde C, Lund LH. Women have better long-term prognosis than men after cardiac resynchronization therapy. Europace 2012; 14:1148–1155.
24. Mooyaart EA, Marsan NA, van Bommel RJ, Thijssen J, Borleffs CJ, Delgado V, van der Wall EE, et al. Comparison of long-term survival of men versus women with heart failure treated with cardiac resynchronization therapy. Am J Cardiol 2011; 108:63–68.