Cardiac resynchronization therapy : determinants of patient outcome and emerging indications

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Chapter 10

Morbidity and mortality in heart failure patients treated with cardiac resynchronization therapy: influence of pre-implantation characteristics on long-term outcome

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Eur Heart J 2010;31(22):2783-90

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) improves cardiac function, heart failure symptoms and prognosis in selected patients. Many baseline characteristics associated with heart failure may influence prognosis after CRT. Objective of this study was to evaluate the effect of several baseline characteristics in relation to long-term prognosis in heart failure patients treated with CRT.

Methods: A total of 716 consecutive heart failure patients treated with CRT were included in an observational registry. All available data, including clinical and echocardiographic measurements, were analyzed in relation to 2 end-points: all cause mortality and a combined end-point of all cause mortality or major cardiovascular event. Outcome data were collected by chart review, device interrogation and telephone contact.

Results: Mean follow-up was 25±19 months. During follow-up, 141 patients (20%) died (primary end-point). Most of these patients (61%) died due to worsening heart failure. A total of 214 patients (30%) reached the secondary end-point. Larger left-ventricular end-systolic volume, less distance covered in the 6-minute walking test, poor renal function, more severe heart failure, male gender, presence of atrial fibrillation, no posterolateral left ventricular lead and no left ventricular dyssynchrony were associated with poor prognosis after CRT.

Conclusions: In this large single-centre registry, several baseline clinical and echocardiographic characteristics were associated with prognosis after CRT. Worsening heart failure was the main cause of death in heart failure patients treated with CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a well established treatment in selected patients with drug-refractory heart failure. Short term response to CRT has been extensively investigated in several studies.[1-7] Most of these studies demonstrated improvement in clinical symptoms, exercise capacity, quality of life and systolic function. However, little is known about prognosis is these patients and parameters influencing long-term outcome. Thus far, two large randomized trials have demonstrated increased survival and lower incidence of heart failure related hospital admissions in patients treated with CRT as compared to optimal medical treatment.[8, 9] These trials were prospectively designed with many exclusion criteria. Many of these exclusion criteria (e.g. atrial arrhythmias) are common among patients with drug-refractory heart failure that are eligible for CRT.[10, 11] Furthermore, patients in clinical trials are closely monitored and receive a more extensive follow-up than they would in daily routine. To better understand survival benefit in patients treated with CRT we present the results from a large registry of unselected consecutive heart failure patients treated with CRT. We compared outcome between different patient groups and evaluated different predictors for adverse or favorable prognosis in a multivariate model.

METHODS

Patient population and protocol

A total of 716 consecutive patients with moderate to severe heart failure who underwent successful CRT implantation were included in the current registry. Before and 6 months after CRT implantation, all patients underwent extensive clinical and echocardiographic evaluation. Two-dimensional (2D) and Doppler echocardiography was performed before CRT implantation and at 6 months follow-up to evaluate cardiac function and included measurement of left ventricular (LV) volumes and LV ejection fraction (LVEF). Finally, LV dyssynchrony was assessed by tissue Doppler imaging as described previously.[12] After device implantation, LV lead position was determined using biplane fluoroscopy.

After the 6 months follow-up, patients were scheduled for regular visits to the outpatient clinic.

Clinical evaluation

Clinical assessment consisted of classification of heart failure symptoms according to the New York Heart Association (NYHA). Assessment of quality of life was performed using the Minnesota Living with Heart Failure Questionnaire (higher scores indicating poorer quality of life)[13] and exercise capacity was measured using the 6-minute walk test.[14]

Echocardiographic evaluation

All patients underwent echocardiography in the left lateral decubitus position before and six months after CRT implantation. Imaging was performed using a commercially available echocardiographic system (VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber images) views. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cineloop format. A minimum of three consecutive beats were recorded from each view and the images were digitally stored for off-line analysis (EchoPac 7.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA). Left ventricular end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LVEF were measured from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule.[15] Severity of mitral regurgitation (MR) was assessed according to current guidelines.[16] LV dyssynchrony was defined as ≥65 ms delay between the peak systolic velocities of the basal septal and lateral wall using tissue Doppler imaging.[12]

Device implantation

The LV lead was inserted transvenously via the subclavian route. A coronary sinus venogram was obtained using a balloon catheter. Next, the LV pacing lead was inserted through the coronary sinus with the help of an 8Fr guiding catheter and positioned as far as possible in the venous system, preferably in a (postero-) lateral vein. The right atrial and ventricular leads were positioned conventionally. Fifty-six patients (8%) received CRT without ICD (CRT-P), while 660 patients (92%) received a device with ICD backup (CRT-D). Devices used were: Contak Renewal, Contak TR or Contak CD, Guidant USA, InSync Marquis, InSync III or InSync Sentry, Medtronic Inc. USA, Epic HF or Atlas HF, St. Jude Medical USA and Lumax 340, Biotronik, Germany. The LV lead position was determined using biplane fluoroscopy classification, as described previously.[17]

Data collection, long-term follow-up and end-points

Outcome data were collected by chart review, device interrogation and telephone contact. Deaths were classified as cardiac, non-cardiac and unknown. Cardiac deaths were sub-classified as sudden death (not preceded by worsening heart failure), death due to (worsening) heart failure or other cardiac deaths (including death related to a procedure, e.g. cardiac surgery or ablation and death after endocarditis). Non-cardiac deaths included all other deaths of known, but non-cardiac cause. Other events included hospitalization for worsening heart failure, hospitalization for ventricular arrhythmias, cardiac surgery, myocardial infarction, PCI and cardiac device infection. Elective replacement of the device due to discomfort or battery depletion and relocation of the LV lead were not included in the analyses. Patients who underwent heart transplantation were withdrawn from further analysis at the time of transplantation.

To facilitate comparison of the current data with that of other trials, end-points for this study were chosen similarly to those used in CARE-HF.[9] Primary end-point was death from any cause. Secondary end-point was a composite of death from any cause or an unplanned hospitalization for a major cardiovascular event.

Statistical analysis

Continuous data were not normally distributed as evaluated with the Kolmogorov-Smirnov test and therefore presented as medians and corresponding 25^{th} and 75^{th} percentiles (data presented between brackets in the results section). Dichotomous data are presented as numbers and percentages. Fisher's exact tests or χ^2 tests were used as appropriate to compare dichotomous data. Comparison of data within patient groups (at baseline and 6 months follow-up) was performed with the Mann-Whitney U-test. The (event-free) survival of patients was evaluated with the Kaplan-Meier method. The effect of different variables on (event-free) survival was investigated using the Cox proportional hazards model. Variables that showed a statistically significant effect on (event-free) survival in univariate analyses were entered in a multivariate Cox proportional hazards model using a backward stepwise selection to obtain the final model. At each step, the least significant variable was discarded from the model, until all variables in the model reached a p-value below 0.25. The number of variables that could enter the multivariate was limited using the P <m/10 rule to prevent over-fitting the model. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). All statistical tests were 2-sided. A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Seven hundred and sixteen patients were included in this analysis. Baseline characteristics of these patients are summarized in Table 1. Patients had severely depressed LV function, with a mean LVEF of 25% (19 – 31). Ischemic cardiomyopathy was the underlying cause of heart failure in 424 (59%) patients. Five hundred and forty patients (75%) were in sinus rhythm at

Table 1. Patient characteristics (n = 716)

Age (years), 25th-75th percentiles	67 (59 – 74)
Gender M / F	566 / 150
Cause (n)	
Ischemic	424 (59%)
Nonischemic	292 (41%)
QRS duration (ms), 25th-75th percentiles	160 (136 – 179)
Rhythm (n)	
Sinus rhythm	540 (75%)
Atrial fibrillation	99 (14%)
Paced	77 (11%)
LBBB	422 (59%)
NYHA functional class (n)	
II	146 (20%)
III	515 (72%)
IV	55 (8%)
6 MWT (m), 25th-75th percentiles	306 (230 – 380)
QoL score, 25th-75th percentiles	37 (24 – 50)
Diabetes (n)	145 (20%)
eGFR (ml/min/1.73m^2), 25th-75th percentiles	65 (47 – 85)
LVEDV (ml), 25th-75th percentiles	212 (165 – 267)
LVESV (ml), 25th-75th percentiles	159 (117 – 207)
LVEF (%), 25th-75th percentiles	25 (19 – 31)
MR grade (0 / 1 / 2 / 3 / 4)	97 / 280 / 216 / 87 / 36
LV dyssynchrony, 25th-75th percentiles	80 (30 – 109)
LV dyssynchrony ≥65ms	495 (69%)
Medication (n)	
Anticoagulants	660 (92%)
Diuretics	615 (86%)
ACE-inhibitors/AII-blocker	639 (89%)
B-blockers	493 (69%)
Spironolactone	356 (50%)

6 MWT = 6-Minute Walk Test; ACE = angiotensin-converting enzyme; eGFR = estimated Glomerular filtration rate; LBBB = Left Bundle Branch Block; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association

the time of device implantation. Seventy-seven patients (11%) had previously undergone pacemaker implantation and were upgraded to a biventricular device.

Clinical response and LV reverse remodeling after CRT

At 6 months, mean NYHA functional class improved from 3 to 2 (2 – 3), p<0.001. In addition to NYHA functional class, quality of life score decreased from 37 (24 – 50) to 21 (10 – 37), p<0.001, while distance covered in the 6-minute walk test increased from 306 m (230 – 380) to 390 m (315 – 453), p<0.001. Also, improvement in LV function was noted after 6 months. LVESV decreased from 159 ml (117 – 207) to 127 ml (99 – 174), while LVEDV decreased from 212 ml (165 – 267) to 186 ml (142 – 238), both p<0.001 (Figure 1, Panel A and B). Consequentially, an increase in LVEF from 25% (19 – 31) at baseline to 32% (25 – 38) at 6 months follow-up was observed, p<0.001 (Figure 1, Panel C).

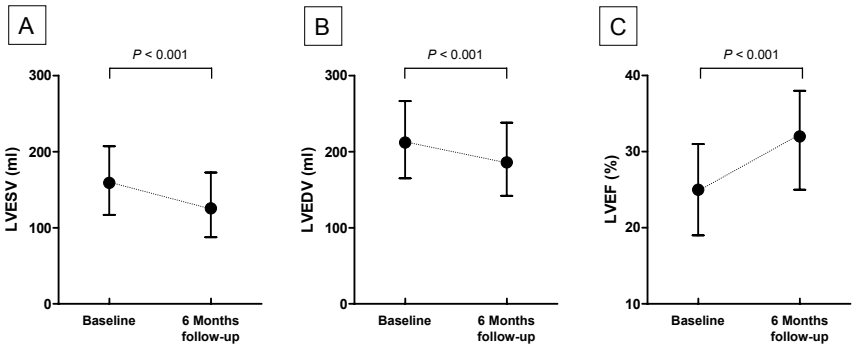

Figure 1. Echocardiographic changes at 6 months follow-up. Significant improvements in left ventricular (LV) end-systolic volume (LVESV, panel A), LV end-diastolic volume (LVEDV, panel B) and LV ejection fraction (LVEF, panel C) were observed at 6 months follow-up. Provided p-values are for comparison between baseline and 6 months follow-up.

Long-term outcome

Mean follow-up of all 716 patients was 25±19 months. During follow-up, 141 patients (20%) died and therefore reached the primary end-point. Three patients underwent heart transplantation. These patients were censored from further analysis at the day of transplantation. The survival curve for time to all-cause mortality (the primary end-point) is displayed in Figure 2. One- and two-year mortality rates were 8.1% and 16.1% respectively. In 86 patients (61%), worsening heart failure was the cause of death. Seventeen patients (12%) died suddenly. Of note, 3 of these patients (18%) received a CRT-P device, while 14 patients (82%) received a CRT-D device. Finally, 11 patients (8%) died of other cardiac causes (3 due to acute myocardial infarction, 2 died due to endocarditis and 6 during or shortly after cardiac surgery). The remaining 27 patients died of non-cardiac causes (8 died of sepsis, 12 due to a malignancy, 1 after a massive cerebrovascular accident, 2 due to a rupture of an abdominal aortic aneurysm and 1 after abdominal surgery). In 3 patients the cause of death could not be determined using all available resources and were therefore also classified as non-cardiac. Separate survival curves for time to each cause of death are provided in Figure 3. Secondary end-point was a composite of death from any cause or an unplanned hospitalization for a major cardiovascular event. During follow-up, a total of 214 patients (30%) reached this secondary end-point. The curve for time to the secondary end-point is shown in Figure 4. Of note, 48 patients (6.7%) required LV lead intervention (LV lead replacement or LV lead repositioning) during follow-up, and 16 patients (2.3%) had a pocket infection that required extraction of the CRT system.

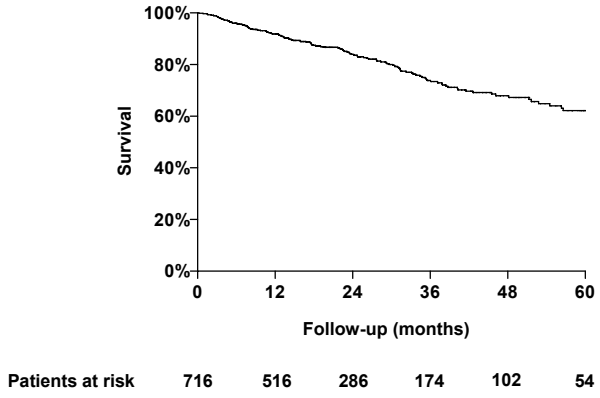

Figure 2. Kaplan-Meier survival curve for time to all-cause mortality. Respective 1- and 2-year mortality rates were 8.1% and 16.1%.

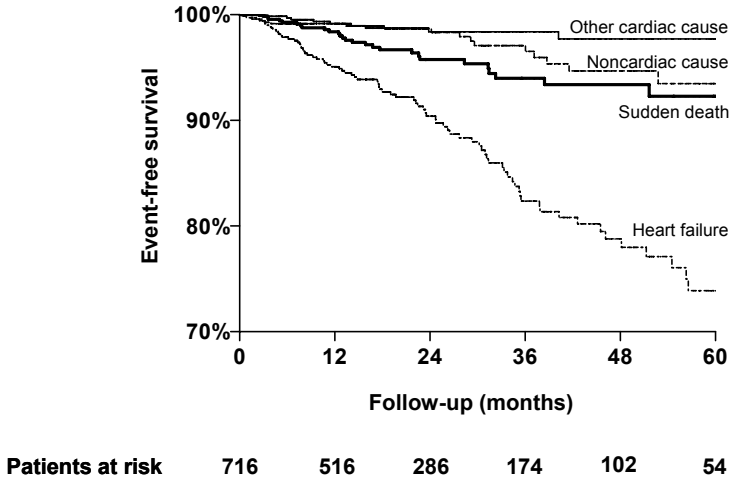

Figure 3. Kaplan-Meier survival curves for time to death from different causes. With 61% of total deaths, worsening heart failure was the main cause of death. A total of 17 patients (12%) died suddenly, 11 patients (8%) died of other cardiac causes and 27 patients died of non-cardiac causes.

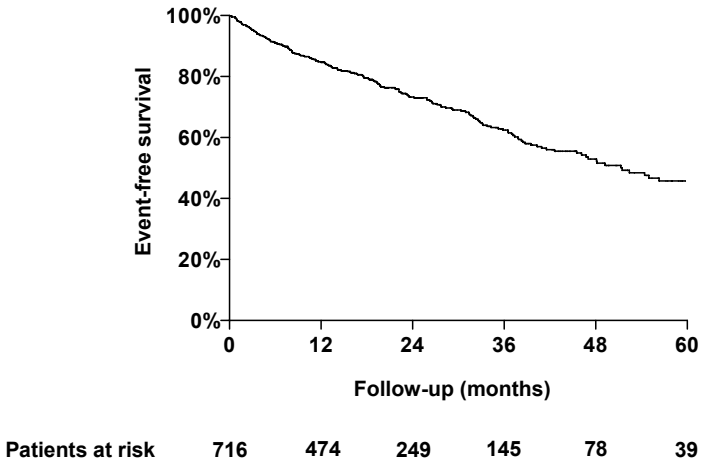

Figure 4. Kaplan-Meier curve for time to death from any cause or unplanned hospitalization for any major cardiovascular event. A total of 214 patients (30%) reached the secondary end-point during follow-up.

Finally, 17 patients with atrial fibrillation (17%) underwent atrioventricular node ablation during long-term follow-up.

Difference in long-term outcome between patient sub-groups and predictors of long-term prognosis

Univariate and multivariate hazard ratios (HR) and corresponding 95% confidence intervals (C.I.) for the primary and secondary end-points are displayed in Tables 2a and 2b respectively. Results for multivariate analysis were as follows: for the primary end-point, lower glomerular filtration rate at baseline was strongly predictive for adverse outcome, with a HR of 1.18 per decrease of 10 ml/min/1.73m^2 (95% C.I. 1.09 – 1.27, p<0.001). Also distance covered in the 6-minute walk test, male gender, increased LVESV and presence of atrial fibrillation were predictive for reduced survival probability after CRT, with a HR of 1.16 per 50 m decrease in the 6-minute walk test (95% C.I. 1.08 – 1.26, p<0.001), a HR of 1.64 (95% C.I. 1.02 – 2.64, p = 0.043) for men vs. women, a HR of 1.03 per 10 ml increase in baseline LVESV (95% C.I. 1.01 – 1.06, p = 0.005) and finally, a HR of 1.78 (95% C.I. 1.14 – 2.78, p = 0.011) for presence of atrial fibrillation. A posterolateral LV lead and the presence of significant LV dyssynchrony were also associated with improved survival after CRT, with a HR of 0.56 (95% C.I. 0.38 – 0.82, p = 0.003) and 0.65 (95% C.I. 0.46 – 0.92, p = 0.016) respectively (Table 2a).

Multivariate analysis was also performed for the secondary end-point (death or unplanned hospitalization after CRT). In this analysis, again lower glomerular filtration rate and the presence of atrial fibrillation proved to be very strong predictors of adverse outcome, with a HR of 1.10 per decrease of 10 ml/min/1.73m^2 (95% C.I. 1.03 – 1.16, p = 0.003) and a HR of 1.71 (95% C.I. 1.19 – 2.46, p = 0.004) respectively. Other significant predictors for reaching the secondary end-point included male gender, ischemic cardiomyopathy, diabetes, higher NYHA functional class, more severe MR, no LV dyssynchrony and no posterolateral LV lead (Table 2b).

Table 2a. Predictors of all-cause mortality risk, uni- and multivariate Cox proportional hazards models

	Univariate		Multivariate	
	HR (95%-C.I.)	*p-value*	*HR (95%-C.I.)*	*p-value*
Age (years)	1.04 (1.02-1.06)	**<0.001**		
Male gender	1.63 (1.01-2.64)	**0.044**	1.64 (1.02-2.64)	**0.043**
Ischemic cardiomyopathy	1.54 (1.07-2.23)	**0.020**	1.32 (0.91-1.91)	0.141
Diabetes	1.80 (1.21-2.67)	**0.004**	1.40 (0.94-2.08)	0.096
eGFR (per 10 ml/min/1.73m^2 decrease)	1.28 (1.18-1.38)	**<0.001**	1.18 (1.09-1.27)	**<0.001**
Atrial fibrillation	2.74 (1.78-4.24)	**<0.001**	1.78 (1.14-2.78)	**0.011**
QRS duration (per 10 ms increase)	1.01 (0.95-1.07)	0.756		
LBBB	1.16 (0.80-1.68)	0.440		
NYHA functional class	2.26 (1.60-3.19)	**<0.001**		
6 MWT (per 50 m decrease)	1.23 (1.14-1.33)	**<0.001**	1.16 (1.08-1.26)	**<0.001**
LVEDV (per 10 ml increase)	1.01 (0.99-1.03)	0.194		
LVESV (per 10 ml increase)	1.02 (1.00-1.05)	**0.029**	1.03 (1.01-1.06)	**0.005**
LVEF (per % increase)	0.96 (0.93-0.98)	**<0.001**		
MR grade	1.50 (1.22-1.86)	**<0.001**	1.16 (0.99-1.37)	0.070
LV dyssynchrony	0.68 (0.48-0.96)	**0.027**	0.65 (0.46-0.92)	**0.016**
Posterolateral LV lead	0.51 (0.35-0.73)	**<0.001**	0.56 (0.38-0.82)	**0.003**

6 MWT = 6-Minute Walk Test; C.I. = confidence interval; eGFR = estimated Glomerular filtration rate; LBBB = Left Bundle Branch Block; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association

Table 2b. Predictors of all-cause mortality or unplanned hospitalization for any major cardiovascular event risk, uni- and multivariate Cox proportional hazards models

	Univariate		Multivariate	
	HR (95%-C.I.)	*p-value*	*HR (95%-C.I.)*	*p-value*
Age (years)	1.02 (1.01-1.04)	**0.001**		
Male gender	1.54 (1.05-2.25)	**0.026**	1.53 (1.05-2.25)	**0.028**
Ischemic cardiomyopathy	1.60 (1.18-2.16)	**0.002**	1.44 (1.07-1.94)	**0.017**
Diabetes	1.79 (1.29-2.48)	**0.001**	1.55 (1.13-2.12)	**0.007**
eGFR (per 10 ml/min/1.73m^2 decrease)	1.19 (1.12-1.27)	**<0.001**	1.10 (1.03-1.16)	**0.003**
Atrial fibrillation	2.21 (1.51-3.24)	**<0.001**	1.71 (1.19-2.46)	**0.004**
QRS duration (per 10 ms increase)	1.03 (0.98-1.08)	0.278		
LBBB	1.22 (0.90-1.66)	0.204		
NYHA functional class	2.11 (1.58-2.80)	**<0.001**	1.44 (1.03-2.02)	**0.033**
6 MWT (per 50 m decrease)	1.13 (1.06-1.20)	**<0.001**	1.05 (0.98-1.13)	0.155
LVEDV (per 10 ml increase)	1.01 (0.99-1.03)	0.252		
LVESV (per 10 ml increase)	1.02 (1.00-1.04)	0.060		
LVEF (per % increase)	0.97 (0.95-0.99)	**0.001**	0.99 (0.97-1.01)	0.185
MR grade	1.37 (1.22-1.54)	**<0.001**	1.32 (1.16-1.50)	**<0.001**
LV dyssynchrony	0.70 (0.53-0.92)	**0.011**	0.69 (0.52-0.91)	**0.009**
Posterolateral LV lead	0.56 (0.41-0.76)	**<0.001**	0.67 (0.48-0.92)	**0.013**

6 MWT = 6-Minute Walk Test; C.I. = confidence interval; eGFR = estimated Glomerular filtration rate; LBBB = Left Bundle Branch Block; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association

DISCUSSION

The main finding of the current registry is that long-term prognosis in terms of survival in this population is similar to that reported in CARE-HF, with one and two year mortality rates of 8.1% and 16.1% respectively in the current study vs. 8.6% and 17% respectively in CARE-HF. Worsening heart failure was the main cause of death during follow-up.

In large clinical studies, patients must meet several inclusion criteria before trial enrolment. Moreover, many exclusion criteria exist so that patients in these trials may not represent the entire group of patients eligible for treatment. This is also true for trials that investigated the effect of CRT on morbidity and mortality.[8, 9] Based on guidelines derived from these trials, it has been estimated that only 10% of heart failure patients meet the current criteria for CRT,[18] and a more recent study by McAlister et al. reported eligibility as low as 1% of all heart failure patients.[19] Although the authors address some important limitations in their study design, adjusting for these limitations would still lead to eligibility substantially below 10%. It is likely that these heart failure patients, although not being CRT candidates according to current guidelines, could sustain a large benefit from treatment with CRT. Accordingly, the aim of this registry was to investigate long-term prognosis in a large, more heterogeneous cohort of heart failure patients undergoing CRT.

Predictors of mortality: comparison with the general heart failure population

Many of the found characteristics that were associated with mortality after CRT are also considered risk factors in the general heart failure population. First, heart failure patients with renal failure have worse long-term prognosis than patients with preserved renal function.[20-23] Possible explanations for worse outcome in patients with renal failure (apart from associated mortality risk with intrinsic renal disease) may be that renal failure is a result of increased venous pressure, or that it is caused by forward failure due to more severely depressed LVEF, which in turn may result in worse outcome.

A retrospective analysis of the SOLVD study revealed that a 10 ml/min/1.73m^2 lower GFR was associated with a 1.064 higher risk for mortality.[20] The currently observed HR of 1.18 for all-cause mortality is clearly higher than in SOLVD, but may be explained by the fact that SOLVD comprised less sick patients with 86% being in heart failure class I or II according to the NYHA classification, whereas 80% was in class III or IV in the present study. Also, data from the CHARM program revealed that heart failure patients with a GFR below 60 ml/min/1.73m^2 were at an increased risk (HR 1.50) for all-cause mortality, after adjustment for confounding factors.[21] The current results suggest that, although clinical outcome and systolic function improves in heart failure patients treated with CRT, renal failure remains a major contributor

to morbidity and mortality. The effect of medication (e.g. diuretics, angiotensin-converting enzyme inhibitors) on renal function was not evaluated in the current study.

In addition to renal dysfunction, patients with atrial fibrillation showed a 1.9 times increased mortality risk when compared to patients in sinus rhythm. The prognostic value of atrial fibrillation in heart failure patients has been described extensively.[24-26] The SOLVD trial identified atrial fibrillation as an independent risk factor (HR 1.34) for mortality[24] and results from the DIG trial showed that development of any supraventricular tachyarrhythmia was a predictor of total mortality in congestive heart failure, with a HR as high as 2.451.[26] The currently reported hazard ratio of 1.78 is similar to the mortality risk of atrial fibrillation as reported in the Framingham heart study.[27]

Beside these 2 strong predictors of clinical outcome, male gender, larger baseline LVESV and less distance covered in the 6-minute walk test were associated with worse survival after CRT. Large studies have reported better survival for women with heart failure as compared to men.[28-30] Superior 5-year survival for women (35% vs. 25% for men) after diagnosis of heart failure and a consequential age-adjusted HR of 0.64 was reported for women with congestive heart failure by Ho and colleagues,[29] which corresponds well with the HR of 1.64 for men in the presently investigated CRT population.

Furthermore, LVESV is in general a strong predictor of survival in cardiac patients[31] and a recent study by Gradaus et al identified increased baseline LV end-systolic diameter as an independent predictor for worse survival after CRT.[32] This is in line with the current finding that larger LVESV was associated with higher mortality.

Importantly, (significant) LV dyssynchrony was associated with superior outcome after CRT. This is contrary to findings in the general heart failure population, where dyssynchrony is related to worse outcome.[33] However, previous studies have confirmed that LV dyssynchrony is amendable through CRT, resulting in improved outcome in heart failure patients with significant LV dyssynchrony.[34]

Finally, 6-minute walking distance is a good marker for clinical status in heart failure patients[14] and has a high prognostic value for morbidity and mortality in patients with systolic dysfunction. Bittner et al demonstrated that heart failure patients walking less than 300 m had a 3.7-fold risk of dying as compared to patients who walked at least 450 m.[35]

Predictors of mortality: comparison with mid-term response to CRT

Several of the above described predictors for long-term outcome have also been investigated previously with regard to mid-term (6 months) response to CRT. For instance, Fung et al first described that impaired renal function was associated with worse clinical outcome in patients treated with CRT.[36] The authors found that patients with LV reverse remodeling showed a slight improvement in renal function (51.7±20.4 ml/min/1.73m^2 at baseline vs.

54.2±19.1 ml/min/1.73m^2 at 3 months follow-up), while patients without reverse remodeling had a deterioration in renal function (61.9±17 ml/min/1.73m^2 vs. 48.8±13.0 ml/min/1.73m^2, p<0.001). More importantly, patients with deteriorated renal function during follow-up had a higher mortality rate than patients with preserved renal function (HR 1.96, p<0.01). Apart from this study, little is known about the effects of CRT on renal function and further studies are required to investigate the potential beneficial effect of CRT on renal clearance and the forthcoming effect on prognosis.

Also, patients with larger LV volumes have been reported to show less response to CRT. A study by Díaz-Infante in 197 CRT recipients revealed that patients with a left ventricular end-diastolic diameter (LVEDD) ≥75 mm were less likely to demonstrate LV reverse remodeling at 6 months follow-up as compared to patients with a LVEDD <75 mm (HR 3.1, p = 0.026).[37] A possible explanation for this may be the fact that some patients have such dilated ventricles that they are beyond a certain point of no return and that even such an effective therapy as CRT could fail to improve systolic function in these patients, indicating an irreversible process of (negative) remodeling.

Furthermore, a gender difference in response rate exists. Lilli et al noted that after correction for other factors, women demonstrated not only a higher extent of LV reverse remodeling than men after CRT, but that among women there was also a higher percentage who demonstrated significant LV reverse remodeling, defined as a reduction in LVESV ≥10% at 12 month follow-up (76.1% vs. 59.3% in men, p<0.05).[38] In the present study, ischemic etiology of heart failure was observed in 65% of men, vs. 39% of women, p<0.001. This may (partially) explain the observed differences between men and women.

Interestingly, a posterolateral positioned LV lead was associated with superior survival after CRT. Similar findings were reported by Rossillo et al in a retrospective study of 233 patients undergoing CRT.[39] In this study, patients with a (postero-) lateral LV lead had a significant improvement in LVEF (from 19±8% to 27±16%, p = 0.008), while patients with an anterior lead position did not show improvement in LVEF (18±8% vs. 20±10%).

In the current study, (significant) LV dyssynchrony was predictive of improved long-term outcome. The use of mechanical dyssynchrony parameters in CRT remains controversial.[40] Nonetheless, several studies, including CARE-HF, have demonstrated improved survival in CRT recipients with significant dyssynchrony before implantation.[41, 42]

Finally, lower response rates to CRT in patients with atrial fibrillation have been described previously.[3, 43] Gasparini and co-workers demonstrated similar results in 162 patients with chronic atrial fibrillation, treated with CRT, as compared to 511 patients in sinus rhythm, only if atrioventricular junction ablation was performed.[43] In the chronic AF group, there were 48 patients that did not receive atrioventricular junction ablation. These patients did not show improvement in clinical and echocardiographic parameters. A more recent study from the same group also demonstrated a significant survival benefit in CRT for 118 chronic AF patients who were treated with atrioventricular junction ablation as compared to 125 chronic

AF patients where no atrioventricular junction ablation was performed, with an adjusted HR of 0.26 for atrioventricular junction ablation.[44] It cannot be concluded from the current data that the higher mortality rate in patients with atrial fibrillation is due to less response to CRT or that atrial fibrillation itself, as an indicator of progression of disease, was associated with worse survival probability. Nonetheless, previous studies in heart failure patients with AF undergoing CRT suggest that atrioventricular junction ablation is an effective treatment strategy in these patients, since it ensures 100% biventricular pacing.[43, 44] Until today, no large randomized study investigated the effect of atrioventricular junction ablation vs. medication alone in CRT recipients with (chronic) atrial fibrillation.[45]

Conclusion

This is the largest single-centre registry on prognosis in CRT to date. The effect of CRT on morbidity and mortality in patients treated was comparable to that reported in the CARE-HF trial. Worsening heart failure was the main cause of death during follow-up. Moreover, we demonstrated that risk factors in the general heart failure population are also associated with inferior long-term outcome after CRT.

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