CHAPTER 7

Clinical, Echocardiographic, and Neurohormonal Response to Cardiac Resynchronization Therapy: Are They Interchangeable?

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ABSTRACT

Background: The relationship between changes in N-terminal pro-brain natriuretic peptide (NT-proBNP) and echocardiographic or clinical definitions of response to cardiac resynchronization therapy (CRT) has not been evaluated. The aims of the present evaluation were to assess: (1) the relationship between changes in NT-proBNP after 6 months of CRT and clinical and echocardiographic responses; (2) the association between NT-proBNP changes and long-term outcome.

Methods: In 170 patients treated with CRT (age 61 ± 11 years, 75% male), clinical and echocardiographic parameters and circulating NT-proBNP levels were assessed at baseline and 6 months after CRT. At 6 months follow-up, improvement in New York Heart Association class ≥1 point, decrease in left ventricular end-systolic volume ≥15%, and decrease in NT-proBNP ≥15% defined clinical, echocardiographic, and neurohormonal CRT response, respectively. All-cause mortality data were collected and related to neurohormonal response.

Results: Neurohormonal, echocardiographic, and clinical response rates were 54%, 58%, and 66%, respectively. The majority of patients (71%) showing echocardiographic response had NT-proBNP reduction ≥15%. In contrast, only 58% of patients who showed clinical response also had NT-proBNP reduction ≥15%. During a median follow-up of 32 months, 40 patients died. Patients with neurohormonal response demonstrated a superior long-term outcome compared to patients without neurohormonal response (log-rank p=0.02).

Conclusions: NT-proBNP reduction ≥15% showed better agreement with echocardiographic response compared to clinical response. Neurohormonal response was associated with superior long-term outcome compared to insufficient reduction in NT-proBNP levels.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective therapy in selected patients with heart failure inducing significant improvements in clinical symptoms, long-term morbidity, and mortality.[1-3] More importantly, CRT has shown to prevent progression of heart failure by slowing or reversing the left ventricular (LV) remodeling process.[2,4] Neurohormonal activation influences this remodeling process.[5] In recent years, brain natriuretic peptide (BNP) and its amino-terminal portion (NT-proBNP) have emerged as diagnostic and prognostic surrogates in heart failure patients.[6-8] BNP is secreted by the cardiac myocytes in response to pressure or volume overload and counterbalances the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin-angiotensin-aldosterone system and the increased sympathetic autonomic tone.[7] BNP and NT-proBNP circulating levels increase along with progression of heart failure and, therefore, may be considered as biomarkers of LV remodeling. In addition, several heart failure therapies such as CRT may induce significant reductions in NT-proBNP levels which have been associated with long-term prognosis.[9]

So far, response to CRT has been defined by clinical or echocardiographic endpoints such as improvement in New York Heart Association (NYHA) functional class, 6-minute walked distance, or LV reverse remodeling.[10] However, changes in clinical symptoms have repeatedly shown to be a suboptimal surrogate of CRT effects.[11] In addition, several studies have shown significant decreases in NT-proBNP levels after CRT, suggesting that CRT targets the underlying mechanisms of LV remodeling and heart failure.[9,12] So far, the correlation between echocardiographic response to CRT and changes in neurohormonal status has not been studied extensively. Characterization of the relationship between clinical, echocardiographic, and neurohormonal parameters may provide important prognostic information on the effects of CRT in heart failure. Therefore, the objective of the current evaluation was twofold: (1) to assess the relationship between changes in NT-proBNP and clinical and echocardiographic response to CRT in heart failure patients; and (2) to evaluate the long-term outcome in patients with and without neurohormonal response to CRT.

METHODS

Patient Population and Data Collection

Between September 2005 and February 2011, a total of 835 patients received a CRT. From this cohort, moderate and severe chronic heart failure patients who had measurements of NT-proBNP circulating levels at baseline and 6 months follow-up were included in the present evaluation.[13] According to the institutional protocol, prior to CRT implantation, all patients underwent extensive clinical and echocardiographic evaluation.[14] Medical therapy was optimized in all patients, following current guidelines.[13] At 6 months follow-up, clinical

and echocardiographic evaluations were repeated. All clinical and echocardiographic data were entered into the departmental cardiology information system (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and analyzed retrospectively. The Institutional Review Board of the Leiden University Medical Center approved this retrospective evaluation of clinically collected data and waived the need for written informed consent.

The agreement between clinical, echocardiographic, and neurohormonal response to CRT was evaluated. Furthermore, the differences in long-term mortality and hospitalization for heart failure were evaluated in patients with and without neurohormonal response to CRT.

Clinical Data

Heart failure patients were evaluated and treated according to the MISSION! Heart failure protocol, an outpatient and inpatient clinical framework that follows the most recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for heart failure.[13-15] Clinical variables, NYHA functional class, quality of life score (according to the Minnesota Living with Heart Failure questionnaire), and 6-minute walked distance were collected at baseline and at 6 months follow-up. Patients were classified as clinical responders to CRT based on improvement in NYHA functional class by ≥1 point at 6 months follow-up.[16]

Echocardiography

Two-dimensional echocardiographic data were acquired at rest with the patient in left lateral decubitus position using a commercially available system (Vivid 7 and E9, General Electric-Vingmed, Horten, Norway). M-mode, two-dimensional and color, continuous, and pulsed-wave Doppler data were obtained from the parasternal and apical views with a 3.5-MHz transducer and stored in cine-loop format for subsequent analysis with dedicated software (EchoPAC version 111.0.0, General Electric-Vingmed, Horten, Norway).

LV end-systolic and LV end-diastolic volumes were quantified in the apical 2- and 4-chamber views using the biplane Simpson's technique and LV ejection fraction was calculated.[17] Moreover, the severity of mitral regurgitation was assessed with color and continuous wave Doppler echocardiography and scored according to current recommendations of the American Society of Echocardiography.[18] Echocardiographic response to CRT was defined by a reduction of ≥15% in LV end-systolic volume at 6 months follow-up.[19]

NT-proBNP Levels

Blood samples were acquired from peripheral venous blood with the patient at rest. The samples were stored at –80°C. Serum concentrations of NT-proBNP were determined by using proBNP and proBNP II kits from Roche Diagnostics on a Modular Analytics E170

analyzer (Roche Diagnostics, Mannheim, Germany). A "sandwich"-type quantitative immunoassay was performed using antibodies against epitopes in the amino-terminal part of pro-BNP. The lower detection limit was 5 pg/mL. Total coefficients of variance at low concentrations (77 pg/mL) and high concentrations (2,170 pg/mL) were both 2.7%. NT-proBNP levels <125 pg/mL exclude cardiac dysfunction with a high level of certainty in patients with symptoms suggestive of heart failure or dyspnea.[20] In the present evaluation, only patients with available levels of NT-proBNP were included. A decrease in NT-proBNP levels of ≥15% at 6 months of follow-up defined the neurohormonal response to CRT.[21]

CRT Implantation

Implantation of the CRT device was performed through transvenous approach. The right atrial and right ventricular leads were positioned in the atrial appendage and ventricular apex, respectively. A balloon catheter was used to obtain a coronary sinus venogram to identify the most appropriate vein to insert the LV pacing lead (preferably posterolateral vein) (Easytrak, Guidant Corp., St. Paul, MN, USA; Attain, Medtronic Inc., Minneapolis, MN, USA; or Corox, Biotronik GmbH, Berlin, Germany). Finally, the leads were connected to a dedicated CRT device (Contak Renewal, Guidant Corp.; Insync III or Insync Sentrym Medtronic Inc.; or Lumax, Biotronik).

Follow-Up

According to the institutional protocol, all patients were scheduled for 6-month and annual visits at the outpatient clinic. Events after CRT implantation, including all-cause mortality and hospitalization for heart failure, were recorded in the departmental cardiology information system (EPD-Vision®). The primary endpoint was all-cause mortality during long-term follow-up (until October 2011) with the initial time set at 6 months after device implantation. By reviewing medical records the cause of death was collected. The secondary endpoint was defined by a composite endpoint of all-cause mortality or hospitalization for heart failure during follow-up (until October 2011) with the initial time set at 6 months after the device implantation. Lost to follow-up was considered in patients without data on the last 6 months. Data of these patients were included up to the last date of follow-up.

Statistical Analysis

Continuous data are expressed as mean ± standard deviation or median with 25th and 75th percentiles where appropriate and were compared with the Student's *t*-test. Categorical data are expressed as frequencies and percentages and were compared with the χ^2 test. Comparisons between baseline and follow-up were performed with the two-sided Student's *t*-test for paired data. To obtain a Gaussian distribution, NT-proBNP and creatinine values were 10-log-transformed to perform comparisons between patients with and without neurohormonal response to CRT. In addition, 10-log-transformed NT-proBNP values

were used for the comparison between baseline and 6 months follow-up. To assess the agreement between the different definitions of response, the odds ratio and φ-coefficient were used. Using the method of Kaplan-Meier, event rates of the primary and secondary endpoints were analysed with the initial time set at 6 months after the device implantation in patients with and without neurohormonal response to CRT, in patients with and without echocardiographic response to CRT and in patients with and without clinical response to CRT. The groups were compared using the log-rank test. Relative risks, expressed as hazard ratios (HRs) with associated 95% confidence intervals (CIs), were derived from Cox regression models. Multivariate Cox proportional-hazards analyses were performed to evaluate the independent association between neurohormonal, echocardiographic, and clinical response to CRT and the primary and secondary endpoints adjusted for predetermined variables (age, etiology of heart failure, QRS duration, and severity of mitral regurgitation at baseline). To evaluate the relative merits of neurohormonal and echocardiographic response to CRT, the Harrell's *c*-statistic for each model was calculated.

All statistical tests were two-sided and a p-value <0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS software (version 17.0, IBM Corp., Armonk, NY, USA).

RESULTS

Baseline Characteristics

A total of 170 heart failure patients (61 ± 11 years, 75% men) with available NT-proBNP circulating levels at baseline and 6 months follow-up were evaluated. Baseline characteristics of the study cohort and patients without NT-proBNP data are further detailed in Table S1. Patients in the study cohort were younger and demonstrated higher quality of life scores and 6-minute walked distances compared to patients without measurement of NT-proBNP levels. Furthermore, hyperlipidemia was less frequently noted and diabetes was more frequently noted in the study cohort. No differences were observed in gender, NYHA functional class, etiology of heart failure, medical treatment, and echocardiographic parameters. Table 1 summarizes the baseline characteristics of the patient population. In total, 74% of the patients were in NYHA functional class III or IV. Mean LV ejection fraction was 27 ± 7% and the mean QRS duration was 154 ± 30 ms. The etiology of heart failure was ischemic in 110 patients (65%). Medical treatment included diuretics (83%), β-blockers (76%), angiotensin converter-enzyme inhibitors or angiotensin II receptor blockers (93%), and spironolactone (49%). Moderate or severe mitral regurgitation was observed in 33 patients (19%). Laboratory tests showed a mean creatinine of 114 ± 48 μmol/L, mean hemoglobin of 8.6 ± 1.1 mmol/L, and mean NT-proBNP of 2,862 ± 7,090 pg/mL.

Clinical, Echocardiographic, and Neurohormonal Response to CRT

At 6 months follow-up, significant improvements in NYHA functional class (from 2.76 ± 0.56 to 2.16 ± 0.75, p<0.001), quality of life score (from 34 ± 19 to 27 ± 20, p<0.001), and 6-minute walked distance (from 351 ± 136 m to 372 ± 130 m, p=0.01) were demonstrated in the overall population. On the basis of the prespecified definition of clinical CRT response, the percentage of responders was 66% (n=113).

The repeat echocardiogram at 6 months follow-up showed a significant reduction in LV volumes (LV end-systolic volume: from 145 ± 59 mL to 122 ± 54 mL, p<0.001; LV end-diastolic volume: from 197 ± 69 mL to 178 ± 64 mL, p<0.001) and a significant improvement in LV ejection fraction (from 27 ± 7% to 33 ± 9%, p<0.001). A total of 98 patients (58%) showed ≥15% LV end-systolic volume reduction and were considered echocardiographic responders.

Finally, a significant reduction in NT-proBNP levels was observed (log-transformed values: from 3.19 ± 0.44 to 3.04 ± 0.54, p<0.001; nonlog-transformed values: from 2,862 ± 7,090 pg/mL to 2,134 ± 2,783 pg/mL). When a definition of CRT response of ≥15% reduction in NT-proBNP levels was applied, 92 patients (54%) were classified as responder.

Table 1. *Baseline characteristics*

	All patients (n=170)	NT-proBNP reduction (n=92)	No NT-proBNP reduction (n=78)	p*
Clinical characteristics				
Age (years)	61 ± 11	61 ± 12	62 ± 10	0.63
Men, n (%)	128 (75%)	72 (78%)	56 (72%)	0.33
QRS duration (ms)	154 ± 30	160 ± 33	147 ± 24	0.004
QRS morphology, n (%)				0.08
LBBB	111 (65%)	57 (62%)	54 (69%)	
RBBB	8 (5%)	3 (3%)	5 (6%)	
IVCD	21 (12%)	9 (10%)	12 (15%)	
Narrow	8 (5%)	6 (7%)	2 (3%)	
VP	22 (13%)	17 (19%)	5 (6%)	
NYHA class III/IV, n (%)	117 (69%)/8 (5%)	59 (64%)/4 (4%)	58 (74%)/4 (5%)	0.11
QoL score	34 ± 19	31 ± 19	37 ± 18	0.05
6MWT (m)	353 ± 132	366 ± 135	339 ± 128	0.19

Table 1. *Baseline characteristics (continued)*

	All patients (n=170)	NT-proBNP reduction (n=92)	No NT-proBNP reduction (n=78)	p*
Heart failure etiology, n (%)				0.62
Ischemic	110 (65%)	58 (63%)	52 (67%)	
Nonischemic	60 (35%)	34 (37%)	26 (33%)	
Medical history, n (%)				
Hypertension	75 (44%)	40 (44%)	35 (45%)	0.91
Hyperlipidemia	65 (39%)	36 (40%)	29 (37%)	0.75
Diabetes	48 (28%)	26 (28%)	22 (28%)	0.99
Family history for CAD	79 (47%)	37 (41%)	42 (55%)	0.08
Previous myocardial infarction	86 (51%)	46 (50%)	40 (51%)	0.87
Medication, n (%)				
ACE-inhibitors/ARBs	158 (93%)	84 (91%)	74 (95%)	0.37
β-Blockers	129 (76%)	70 (76%)	59 (76%)	0.95
Aldosterone antagonists	84 (49%)	44 (48%)	40 (51%)	0.65
Statins	121 (71%)	64 (70%)	57 (73%)	0.61
Diuretics	141 (83%)	81 (88%)	60 (77%)	0.06
Echocardiography				
LVESV (mL)	145 ± 58	148 ± 59	142 ± 58	0.52
LVEDV (mL)	197 ± 69	200 ± 69	194 ± 68	0.55
LVEF (%)	27 ± 7	27 ± 7	28 ± 7	0.42
MR grade III/IV, n (%)	29 (17%)/4 (2%)	17 (19%)/2 (2%)	12 (15%)/2 (3%)	0.66
Laboratory tests				
Creatinine (μmol/L)	114 ± 48	114 ± 54	114 ± 39	–
Log creatinine	2.03 ± 0.15	2.02 ± 0.16	2.03 ± 0.14	0.69
Hb (mmol/L)	8.6 ± 1.1	8.5 ± 1.0	8.7 ± 1.1	0.27
NT-proBNP (pg/mL)	2,862 ± 7,090	3,739 ± 9,442	1,828 ± 1,728	–
Log NT-proBNP	3.19 ± 0.44	3.26 ± 0.47	3.10 ± 0.38	0.02

* p-values are given for the comparisons of patients with and without neurohormonal response (NT-proBNP reduction ≥15% at 6 months of follow-up).
6MWT = 6-minute walked test; *ACE* = angiotensin-converting enzyme; *ARBs* = angiotensin receptor blockers; *CAD* = coronary artery disease; *Hb* = hemoglobin; *IVCD* = interventricular conduction delay; *LBBB* = left bundle branch block; *LVEDV* = left ventricular end-diastolic volume; *LVEF* = left ventricular ejection fraction; *LVESV* = left ventricular end-systolic volume; *MR* = mitral regurgitation; *NT-proBNP* = amino-terminal pro-brain natriuretic peptide; *NYHA* = New York Heart Association; *QoL* = quality of life; *RBBB* = right bundle branch block; *VP* = ventricular paced.

In Table 1, baseline characteristics of patients with and without neurohormonal response to CRT (a reduction in NT-proBNP ≥15% at 6 months follow-up) are summarized. At baseline, patients showing neurohormonal CRT response had significantly longer QRS durations (160 ± 33 ms vs 147 ± 24 ms, p=0.004) compared to patients without neurohormonal response. In addition, baseline NT-proBNP circulating levels were significantly higher in patients with neurohormonal response (log-transformed values: 3.26 ± 0.47 vs 3.10 ± 0.38, p=0.02; nonlog-transformed values: 3,739 ± 9,442 pg/mL vs 1,828 ± 1,728 pg/mL).

Neurohormonal Response versus Clinical Response to CRT

In order to evaluate whether the changes in neurohormonal status after CRT implantation reflect the clinical response to CRT, the concordance between clinical and NT-proBNP definitions of response to CRT was assessed (Figure 1). At 6 months follow-up, 58% of patients (n=65 of 113) showing clinical response also showed NT-proBNP response. In contrast, 47% of patients (n=27 of 57) without a clinical improvement did show a reduction in circulating levels of NT-proBNP. A poor association between neurohormonal response and clinical response to CRT was demonstrated; odds ratio is 1.51 (95% CI 0.79–2.85) (φ-coefficient = 0.10, p=0.21).

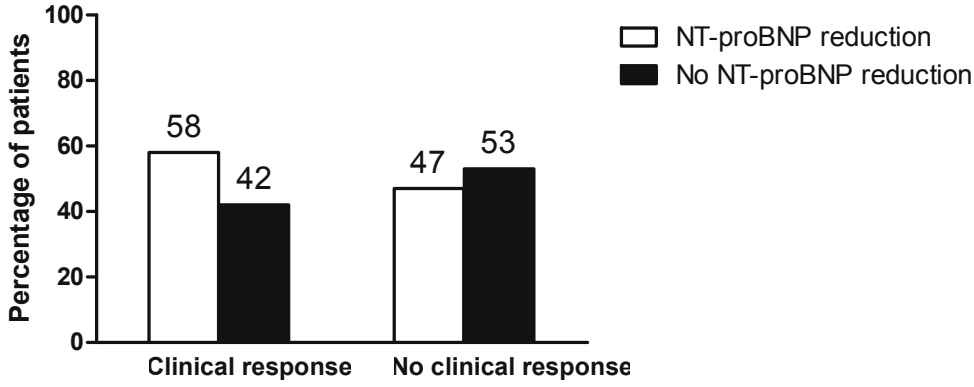

Figure 1. Agreement between two different definitions of response to CRT. The bars show the percentages of patients with concordant or discrepant clinical response, as defined by an improvement of NYHA functional class of ≥1 point, with NT-proBNP response defined as a ≥15% reduction at 6 months of follow-up. *CRT* = cardiac resynchronization therapy; *NYHA* = New York Heart Association; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Neurohormonal Response versus Echocardiographic Response to CRT

Figure 2 shows the concordance between echocardiographic and NT-proBNP definitions of CRT response. Seventy-one percent of patients (n=70 of 98) showing significant LV reverse remodeling also demonstrated a reduction in NT-proBNP ≥15% at 6 months follow-up. In addition, most of the patients who did not show LV reverse remodeling did not exhibit a reduction of ≥15% in NT-proBNP (70%, n=50 of 71). In contrast to the discordance between clinical and neurohormonal definitions of response, only 21 patients who showed significant reduction in NT-proBNP levels did not demonstrate significant LV reverse remodeling, resulting in a disagreement rate of 23%. The association between neurohormonal response and echocardiographic response to CRT was clinically relevant; odds ratio is 5.95 (95% CI 3.04–11.66) (φ-coefficient = 0.41, p<0.001).

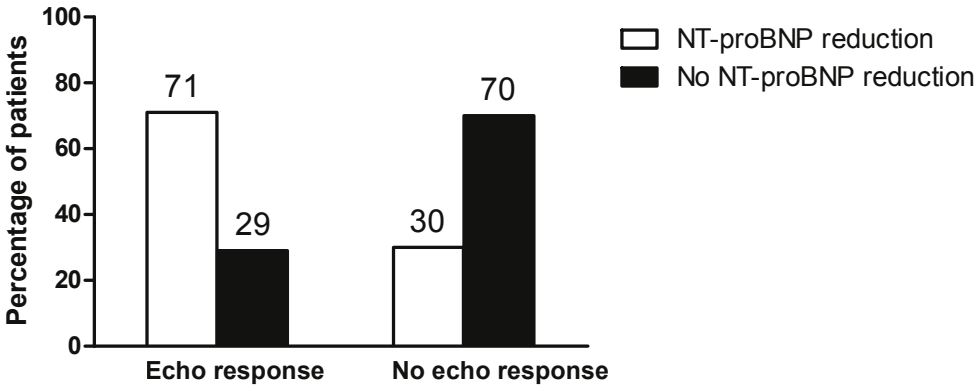

Figure 2. Agreement between two different definitions of response to CRT. The bars show the percentage of patients with concordant or discrepant echocardiographic response, as defined by a decrease of LV end-systolic volume of ≥15%, with NT-proBNP response, defined as a ≥15% reduction at 6 months of follow-up. *CRT* = cardiac resynchronization therapy; *Echo* = echocardiographic; *LV* = left ventricular; *NT-proBNP* = N-terminal pro-brain natriuretic peptide.

Long-Term Follow-Up

Survival analysis was performed with the initial time set at 6 months after the CRT device implantation. Long-term follow-up was completed in 163 patients (96%) with a median follow-up duration of 32 months (interquartile range 17–44 months). Forty patients (24%) died of all-cause mortality and 19% of the patients (n=33) were hospitalized for heart failure during follow-up. The secondary endpoint, a composite of all-cause mortality or hospitalization of heart failure, was reached by 52 patients (31%). Cardiovascular mortality was recorded in 18% of the patients (n=31).

The mortality rates for patients with and without neurohormonal response to CRT are shown in Figure 3A. Patients with neurohormonal response to CRT had a significantly better long-term survival compared to patients without neurohormonal response (log-rank p=0.02). The 12-, 24-, and 36-month survival rates for patients with neurohormonal response were 94%, 89%, and 82%, respectively; in patients without neurohormonal response, the 12-, 24-, and 36-month survival rates were 83%, 75%, and 67%, respectively (Figure 3A). Cumulative event rates for the composite endpoint of all-cause mortality or hospitalization for heart failure in both groups are shown in Figure 3B. The event-free survival rates showed a significantly better long-term outcome in patients with neurohormonal response; 12-, 24-, and 36-month event-free survival were 90%, 84%, and 79% in the responder group versus 75%, 63%, and 58% in the nonresponder group, respectively (Figure 3B, log-rank p=0.003).

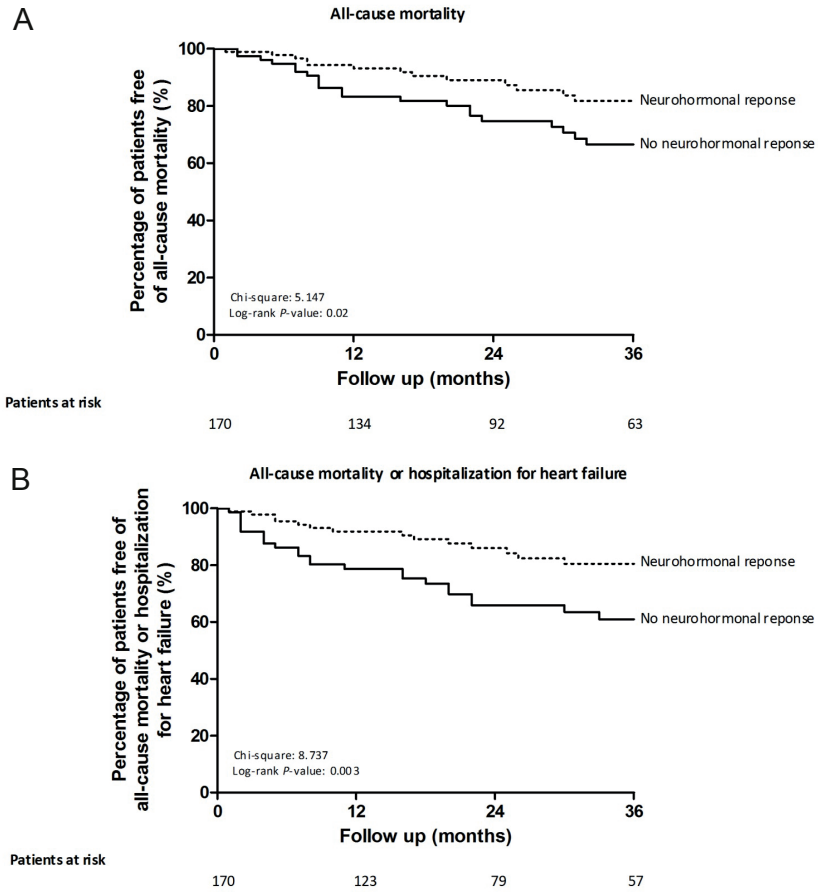

Figure 3. Kaplan-Meier curves estimates of the primary endpoint (all-cause mortality) (A) and secondary endpoint (all-cause mortality or hospitalization for heart failure) (B) in patients with and without neurohormonal response to CRT at 6 months follow-up (defined as: NT-proBNP reduction ≥15%). *CRT* = cardiac resynchronization therapy; *NT-proBNP* = N-terminal pro-brain natriuretic peptide.

Univariate analysis showed that neurohormonal response to CRT was associated with a significant reduced risk of all-cause mortality (HR 0.48, 95% CI 0.26–0.92, p=0.03) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.44, 95% CI 0.25–0.77, p=0.004). After adjusting for clinical and echocardiographic parameters, neurohormonal response to CRT remained independently associated with all-cause mortality (HR 0.39, 95% CI 0.20–0.77, p=0.007) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.36, 95% CI 0.20–0.67, p=0.001). The same results were observed after also adjusting for baseline NT-proBNP levels (all-cause mortality: HR 0.30, 95% CI 0.15–0.61, p=0.001; composite endpoint: HR 0.23, 95% CI 0.12–0.44, p<0.001).

Figure 4 illustrates the cumulative event rates for the primary and secondary endpoints for patients with and without echocardiographic response to CRT. The event-free survival rates showed a significantly better long-term outcome in patients with echocardiographic response (log-rank p=0.001 and p<0.001 for the primary and secondary endpoint, respectively). Univariate analysis demonstrated that echocardiographic response to CRT was associated with a significant reduced risk of all-cause mortality (HR 0.33, 95% CI 0.17–0.64, p=0.001) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.33, 95% CI 0.19–0.58, p<0.001). At multivariate analysis, after adjusting for clinical and echocardiographic parameters, echocardiographic response to CRT remained independently associated with all-cause mortality (HR 0.25, 95% CI 0.12–0.50, p<0.001) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.26, 95% CI 0.15–0.48, p<0.001).

The survival and the event-free survival rates for patients with clinical response to CRT were significantly better compared to patients without clinical response (log-rank p<0.001 and p=0.001 for the primary and secondary endpoint, respectively). At multivariate analysis, after adjusting for clinical and echocardiographic parameters, clinical response to CRT was a strong predictor of long-term outcome, both regarding all-cause mortality (HR 0.29, 95% CI 0.15–0.57, p<0.001) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.40, 95% CI 0.23–0.72, p=0.002). Furthermore, in patients showing clinical response (n=113), the prognostic value of echocardiographic and/or neurohormonal response was evaluated. Clinical responders without echocardiographic or neurohormonal response (n=29) demonstrated a worse long-term outcome compared to clinical responders with echocardiographic and/or neurohormonal response (n=83), both regarding all-cause mortality (log-rank p=0.04) and the composite endpoint (log-rank p=0.002). Also, after correcting for clinical and echocardiographic parameters, clinical response without echocardiographic or neurohormonal response remained independently associated with all-cause mortality (HR 2.82, 95% CI 1.03–7.69, p=0.04) and the composite endpoint (HR 3.38, 95% CI 1.55–7.37, p=0.002).

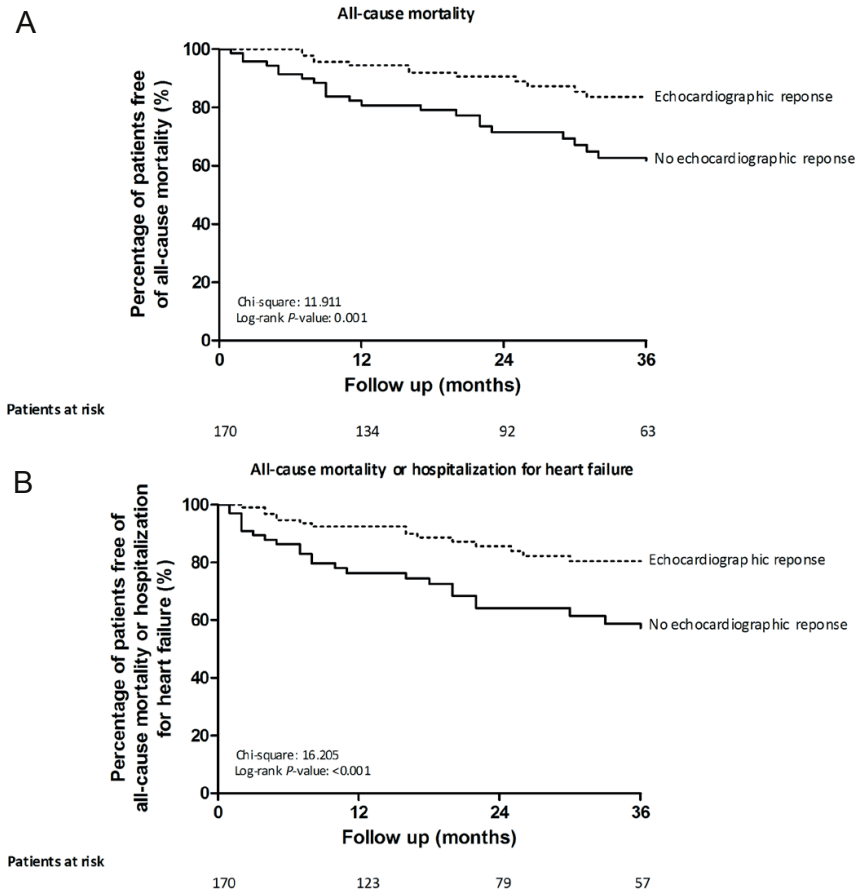

Figure 4. Kaplan-Meier curves estimates of the primary endpoint (all-cause mortality) (A) and secondary endpoint (all-cause mortality or hospitalization for heart failure) (B) in patients with and without echocardiographic response to CRT at 6 months follow-up (defined as: LV end-systolic volume reduction ≥15%). *CRT* = cardiac resynchronization therapy; *LV* = left ventricular.

The relative merits of neurohormonal and echocardiographic responses were assessed calculating the Harrell's *c*-statistic. For the neurohormonal response the Harrell's *c*-statistics of the models were 0.66 and 0.66 for the primary and the secondary endpoint, respectively. For the echocardiographic response the respective Harrell's *c*-statistics for the primary and the secondary endpoint were 0.69 and 0.68.

DISCUSSION

This study demonstrated an agreement of 58% between clinical and neurohormonal response to CRT. In contrast, the agreement between reduction of NT-proBNP and echocardiographic definition of CRT response was 70%, suggesting that an objective evaluation of CRT response may be more accurate than an assessment including clinical

surrogates. In addition, patients with neurohormonal response to CRT at 6 months follow-up showed a better long-term outcome regarding both survival and hospitalization for heart failure.

Defining CRT Response: Subjective Clinical versus Objective Changes in LV Remodeling and Neurohormonal Status

There is no established definition of response to CRT yet. The efficacy of heart failure therapies has been evaluated with improvements in clinical symptoms, LV function, or decrease in NT-proBNP.[22] Ultimately, these improvements should determine a superior long-term outcome. In this regard, several studies have shown that the prognostic implications of therapeutic efficacy based on clinical symptoms are controversial.[11] Ingle et al demonstrated in 1,592 patients with heart failure that the prognostic value of patient-perceived physical symptoms is little in contrast with more objective measures, for example, 6-minute walked distance and NT-proBNP.[11] Although the patient perspective is an important parameter of therapeutic efficacy, objective measures such as LV reverse remodeling may be more accurate.[23] Indeed, definition of the efficacy of heart failure therapies based on LV reverse remodeling and improvement in LV ejection fraction is associated with superior long-term outcome.[22] The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial, for example, including patients with mildly symptomatic heart failure, demonstrated that CRT prevented progression of heart failure and was associated with superior prognosis.[24,25]

In terms of heart failure biomarkers, NT-proBNP circulating levels at baseline have shown to be a powerful prognostic marker in patients with heart failure.[6-8] More importantly, significant decreases in NT-proBNP levels have shown an incremental prognostic value over the baseline levels.[9] In 813 patients undergoing CRT implantation, the Cardiac Resynchronization in Heart Failure (CARE-HF) trial showed that serial assessment of NT-proBNP at baseline and 3 months follow-up was a stronger predictor of all-cause mortality than baseline NT-proBNP.[9] As demonstrated by two other reports of the CARE-HF trial, CRT decreases the circulating levels of NT-proBNP, indicating the value of changes in levels of this biomarker as a measure of efficacy of CRT.[26,27]

However, it remains controversial whether improvements in clinical, echocardiographic, and neurohormonal parameters after CRT implantation may always coincide. This study provides further insights into this issue. A reasonable agreement between neurohormonal changes and echocardiographic response to CRT was observed. In contrast, the agreement between reduction of NT-proBNP and clinical response was poor. These results suggest that clinical, echocardiographic, and neurohormonal parameters of CRT response may reflect different aspects of chronic heart failure. For example, Tarquini et al demonstrated in 47 heart failure patients undergoing CRT implantation that a decrease in activation of renin–angiotensin–aldosterone system was accompanied by LV reverse remodeling at 12 months follow-up.[28] In contrast, patients without LV reverse

remodeling experienced no change in activation of renin-angiotensin-aldosterone system.[28] Moreover, clinical improvement was observed in both echocardiographic responders and nonresponders, implying that assessment of clinical response to CRT may have less value.[28] This was also demonstrated by other studies reporting that CRT reduces NT-proBNP levels in patients with reduction in LV end-systolic volume during 3–6 months follow-up.[21,29]

Neurohormonal Response to CRT and Prognosis

Previous studies already pointed out the use of NT-proBNP levels as marker of response to CRT, especially changes in NT-proBNP levels from baseline.[9,22,26,27] In addition, Magne et al provided a cutoff value for percentage change in NT-proBNP level (a ≥15% reduction) which could accurately predict LV reverse remodeling after CRT implantation.[21] In this study, patients without sufficient reduction in NT-proBNP levels using this cutoff value of 15% had a worse long-term outcome compared to patients with ≥15% reduction in NT-proBNP levels. Therefore, the use of change in NT-proBNP levels may contribute to the evaluation of the effects of CRT.

Definition of CRT Response: Future Directions

Despite the well-known efficacy of CRT, standardized definitions of response to CRT and their prognostic implications have not been established. In this study, echocardiographic and neurohormonal definitions of CRT response showed better agreement than reduction in NT-proBNP and clinical response. The presence of two objective methods to assess CRT efficacy and the agreement between them may select the group of patients who truly respond to CRT. Among patients with discrepant objective responses, further adjustments of medical therapy and CRT device settings may be needed. In this regard, large randomized studies evaluating the effect of CRT settings optimization on LV reverse remodeling and neurohormonal status in patients who do not show benefit from CRT are warranted.

Study Limitations

The present evaluation has some limitations. First, this is a single-center study with a retrospective design. However, all patients were treated and followed according to the most recent heart failure guidelines of American College of Cardiology/American Heart Association and European Society of Cardiology.[13,15] Therefore, this study is representative of current standard clinical practice. Another important limitation of this study is the relatively small sample size that may have precluded us to perform a receiver operating characteristic curve analysis to define the cutoff value of NT-proBNP change to predict response to CRT. In addition, the small sample population may have reduced the accuracy of the model to predict long-term outcome, as reflected by modest Harrell's c-statistics. Furthermore, due to the relatively low number of patients, the results of the present evaluation need to be confirmed in larger populations.

CONCLUSION

Clinical, echocardiographic, and neurohormonal markers of CRT response may reflect different aspects of chronic heart failure. NT-proBNP reduction and LV reverse remodeling after CRT show a better agreement compared to NT-proBNP reduction and clinical response. Furthermore, patients with neurohormonal response show a better long-term outcome compared to patients without neurohormonal response. Our results, therefore, suggest that NT-proBNP in combination with LV reverse remodeling may be more useful to evaluate the effects of CRT in heart failure patients.

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Table S1. *Baseline characteristics of patients included and patients not included in the present evaluation*

	Study cohort (n=170)	No NT-proBNP data (n=665)	p*
Clinical characteristics			
Age (years)	61 ± 11	66 ± 11	<0.001
Men, n (%)	128 (75%)	504 (76%)	0.89
QRS duration (ms)	154 ± 30	152 ± 33	0.45
NYHA class III/IV, n (%)	117 (69%)/8 (5%)	402 (63%)/39 (6%)	0.22
QoL score	34 ± 19	24 ± 21	<0.001
6MWT (m)	353 ± 132	316 ± 114	0.002
Heart failure etiology, n (%)			
Ischemic/nonischemic	110 (65%)/60 (35%)	408 (61%)/257 (39%)	0.42
Medical history, n (%)			
Hypertension	75 (44%)	249 (41%)	0.38
Hyperlipidemia	65 (39%)	228 (49%)	0.02
Diabetes	48 (28%)	136 (21%)	0.03
Medication, n (%)			
ACE-inhibitors/ARBs	158 (93%)	585 (88%)	0.07
β-Blockers	129 (76%)	493 (74%)	0.64
Aldosterone antagonists	84 (49%)	292 (44%)	0.20
Statins	121 (71%)	420 (63%)	0.05
Diuretics	141 (83%)	528 (79%)	0.30
Echocardiography			
LVESV (mL)	145 ± 58	150 ± 62	0.35
LVEDV (mL)	197 ± 69	203 ± 72	0.34
LVEF (%)	27 ± 7	27 ± 8	0.76
Laboratory tests			
Creatinine (μmol/L)	114 ± 48	108 ± 59	–
Log creatinine	2.03 ± 0.15	2.00 ± 0.15	0.05

* p-values are provided for the comparisons of patients with and without measurement of amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels.
6MWT = 6-minute walked test; *ACE* = angiotensin-converting enzyme; *ARBs* = angiotensin receptor blockers; *LVEDV* = left ventricular end-diastolic volume; *LVEF* = left ventricular ejection fraction; *LVESV* = left ventricular end-systolic volume; *NT-proBNP* = amino-terminal pro-brain natriuretic peptide; *NYHA* = New York Heart Association; *QoL* = quality of life.