FACULDADE DE MEDICINA
UNIVERSIDADE D
COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Re-Evaluation of Response to Cardiac Resynchronization Therapy: Long-Term Impact of Echocardiographic Non-Progression

ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE CARDIOLOGIA

Trabalho realizado sob orientação de:

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ABRIL/2023

Re-Evaluation of Response to Cardiac Resynchronization Therapy: Long-Term Impact of Echocardiographic Non-Progression

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The authors declare no conflicts of interest.

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Abstract

Introduction:

In heart failure (HF) with reduced left ventricular ejection fraction (LVEF), the concept that significant left ventricular (LV) reverse remodeling is needed to define “responders” to cardiac resynchronisation therapy (CRT), has been increasingly regarded as an inappropriate assessment of treatment response. Since HF is a progressive disease, patients with a minimal change in LV geometry after CRT, recently defined as “Non-Progressors” or “Stabilisers”, may also derive some benefit from CRT.

The main purpose of this study is to evaluate long-term prognosis of HF patients submitted to CRT, according to pre-specified categories of response based on LV end-systolic volume (LVESV) changes.

Methods:

We included 207 consecutive patients with advanced HF submitted to CRT, according to European recommendations at the time of implantation. The sample was subsequently divided into three groups, based on LVESV variation at six-month follow-up:

- “Responders" (R): ≥15% LVESV reduction;
- “Non-Progressors” (NPr): 0-15% LVESV reduction;
- “Progressors" (Pr): increase in LVESV.

During a mean follow-up time of 54.2 ± 33.1 months, all-cause and cardiovascular (CV) mortality, HF hospitalisations, functional class using New York Heart Association (NYHA) classification and need for cardiac transplantation were evaluated. Predictors of HF progression despite treatment were also assessed.

Results:

At six-month follow-up after CRT, 149 (72.0%) patients showed positive reverse remodeling, with 32 (15.5%) being classified as NPr and 117 (56.5%) as R, while 58 (28.0%) demonstrated increased LVESV, the Pr. Despite clinical, functional and echocardiographic improvement after CRT in the majority of patients, there were statistical differences supporting better functional class response in NPr compared to the Pr. Furthermore, NPr demonstrated a non-significant improvement of all other predefined outcomes compared to the Pr.

Nevertheless, the hazard ratio for time-to-event risk analysis of all-cause mortality and HF hospitalisations showed R with a significantly two-fold risk reduction compared to the Pr and, to a lesser extent yet still approximated, to the NPr.

Ischemic cardiomyopathy, chronic renal disease and NYHA class IV at baseline proved to be statistically significant independent predictors of HF progression.

Conclusion:

In HF patients submitted to CRT, Non-Progressors demonstrated better outcomes, including improved functional class response, than the Progressors. However, regarding survival and HF hospitalisations risk analysis, positive reverse remodeling, and not only stabilisation, seems to be required for improved long-term prognosis with fewer time-to-event risks associated. Ischemic cardiomyopathy, chronic kidney disease and NYHA class IV independently predicted HF progression and therefore worse prognosis despite CRT.

Keywords

HEART FAILURE; CARDIAC RESYNCHRONIZATION THERAPY; LEFT VENTRICULAR REMODELING; MORTALITY; HEART FAILURE HOSPITALISATIONS; CARDIAC TRANSPLANTATION

Resumo

Introdução:

Na insuficiência cardíaca (IC) com fração de ejeção ventricular esquerda reduzida (FEVE), o conceito de que é necessário haver significativa remodelagem inversa do ventrículo esquerdo (VE) para definir uma resposta positiva à terapêutica de ressincronização cardíaca (TRC), tem sido cada vez mais considerado como uma avaliação inadequada de resposta ao tratamento. Considerando que a IC é uma síndrome progressiva, os doentes com alterações mínimas na geometria do VE após TRC, recentemente definidos como “Não Progressores” ou “Estabilizadores”, podem também estar a usufruir de algum benefício da TRC.

O principal objetivo deste estudo é avaliar o prognóstico a longo-prazo de pacientes com IC submetidos à TRC, de acordo com diferentes categorias de variação no volume sistólico final do VE (VSFVE).

Materiais e Métodos:

Incluímos 207 pacientes com IC submetidos à TRC, de acordo com as recomendações europeias no momento da sua implantação. A amostra foi subsequentemente dividida em três grupos, com base na variação do VSFVE ao sexto mês de follow-up:

- "Respondedores" (R): ≥15% de redução do VSFVE;
- "Não-Progressores" (NPr): 0-15% de redução do VSFVE;
- "Progressores" (Pr): aumento do VSFVE.

Durante um follow-up médio de 54,2 ± 33,1 meses, foi avaliada a mortalidade global e cardiovascular (CV), hospitalizações por IC, a resposta através da classe funcional baseada na classificação da New York Heart Association (NYHA) e a necessidade de transplantação cardíaca. Adicionalmente, foram analisados possíveis preditores de progressão da IC, independentemente da TRC.

Resultados:

Ao sexto mês de follow-up após a TRC, 149 (72,0%) doentes mostraram remodelagem inversa, com 32 (15,5%) classificados como NPr e 117 (56,5%) como R, enquanto 58 (28,0%) demonstraram aumento do VSFVE, os Pr. Registou-se uma melhoria clínica, funcional e ecocardiográfica após TRC na maioria dos doentes, com diferenças estatísticas a suportar

uma melhor resposta de classe funcional dos NPr em comparação com os Pr. Além disso, os NPr demonstraram uma melhoria não significativa dos restantes outcomes predefinidos, também em comparação com os Pr. Porém, segundo análise de razão de risco tempo-evento de mortalidade global e hospitalizações por IC, os R mostraram um risco significativo duas vezes menor em comparação com os Pr e, em menor escala ainda assim aproximado, com os NPr.

A cardiomiopatia isquémica, a doença renal crónica e a classe funcional basal NYHA IV provaram ser preditores independentes e estatisticamente significativos de progressão da IC.

Conclusão:

Nos doentes com IC submetidos à TRC, os Não-Progressores apresentaram melhores outcomes, incluindo de resposta funcional, em comparação com os Progressores. No entanto, com base na análise de razão de risco de sobrevivência e hospitalização por IC, a remodelagem inversa, e não apenas a estabilização, parece ser necessária para um melhor prognóstico a longo-prazo com menos riscos tempo-evento associados. A cardiomiopatia isquémica, a doença renal crónica e a classe funcional basal NYHA IV associaram-se a progressão da IC e, como tal a pior prognóstico independentemente da TRC.

Palavras-chave

INSUFICIÊNCIA CARDÍACA; TERAPIA DE RESSINCRONIZAÇÃO CARDÍACA; REMODELAGEM DO VENTRÍCULO ESQUERDO; MORTALIDADE; HOSPITALIZAÇÕES POR INSUFICIÊNCIA CARDÍACA; TRANSPLANTAÇÃO CARDÍACA

List of Abbreviations

bpm beats per minute

CRT cardiac resynchronization therapy

CV cardiovascular

CI confidence interval

HR hazard ratio

HF heart failure

LVEF left ventricle ejection fraction

LV left ventricular / left ventricle

LVESV left ventricular end-systolic volume

NYHA New York Heart Association

NPr Non-Progressors

OR odds ratio

Pr Progressors

R Responders

Introduction

Heart failure (HF) is a highly prevalent syndrome, associated with significant mortality and morbidity. It has an important economic burden to healthcare systems, with increasing rate of hospitalisations and readmissions due to population ageing and its related comorbidities. [1–3]

Despite the advances in pharmacological therapy, the prognosis of these patients remains poor. Medical therapy delays its progression with a five-year mortality rate after diagnosis around 50%, mostly due to sudden cardiac death. [4–7]

In more advanced stages of the disease, non-pharmacological therapies such as cardiac electronic implantable devices, including cardiac resynchronization therapy (CRT), and cardiac transplantation are frequently considered. [8–12]

CRT acts in left ventricular (LV) dyssynchrony which occurs in 30% to 50% of patients with decompensated HF. [13–15] Using biventricular pacing to correct intraventricular dyssynchrony, enables LV reverse remodeling and cardiac output improvement, [4,5,16,17] consequently enhancing patient's hemodynamics and reducing hospitalisations and mortality. [1,8,18–21] However, 30% to 40% of patients with CRT do not show LV reverse remodeling, despite having a functioning device, usually classified as "non-responders". [22,23] Lately, this term has become controversial, given that the intervention will change the progressive rate of the disease, without it being curative. [23–25] Furthermore, considering the natural progression of HF, CRT's role in delaying or suppressing LV remodeling should be deemed as a positive result, even if it does not improve cardiac performance. [26,27]

Our study aims to evaluate whether prognosis differs within different categories of LV reverse remodeling after CRT. We presume that, not only those who have reverse LV remodeling (Responders - "R"), but also patients with a stabilised ventricular volume during treatment (Non-Progressors - "NPr") have better outcomes and longer-term prognosis compared to those with LV remodeling (Progressors - "Pr"). [27] We pursue to compare all-cause and cardiovascular (CV) mortality, HF hospitalisations, functional class using New York Heart Association (NYHA) classification and need for cardiac transplantation, according to these three categories of echocardiographic response to CRT. We also aim to assess baseline characteristics which might trigger worsen responses, leading to HF progression with dismal outcomes despite CRT, to enable better patient selection for the therapy.

Materials and Methods

Study design

We conducted a retrospective observational clinical study, including 207 consecutive patients with advanced HF, with reduced left ventricular ejection fraction (LVEF) and prolonged QRS intervals, who underwent CRT at the Cardiology Department of Centro Hospitalar e Universitário de Coimbra, according to European recommendations at the time of implantation.

The sample was subsequently divided into three groups, according to the left ventricular end-systolic volume (LVESV) variation at six-month follow-up evaluation, based on the following:

- “R” group: ≥15% LVESV reduction;
- “NPr” group: 0-15% LVESV reduction;
- “Pr” group: LVESV increase.

During a mean follow-up time of 54.2 ± 33.1 months, we compared overall and CV mortality, HF hospitalisations, functional class using NYHA classification and need for cardiac transplantation between the groups. Additionally, we evaluated the baseline factors associated with HF progression.

This project respects all legal and ethical standards currently in place. All information provided is true and respects the right to privacy and protection of the participants' personal data, with strict compliance of secrecy and confidentiality. All legal provisions and recommendations of the Helsinki Declaration (1964 and subsequent revisions) and of the World Health Organisation were followed. The protocol was approved by the Ethics Committee of Centro Hospitalar e Universitário de Coimbra (PI OBS.SF.174-2022).

Data collection

Patient selection was carried out by accessing the medical records in the online platforms "SCLÍNICO" and "CARDIOBASE" from Centro Hospitalar e Universitário de Coimbra. Data was stored in an anonymous database on “IBM Statistical Package for the Social Sciences, Statistics version 26” (SPSS inc., Chicago IL., USA).

We included patients submitted to CRT implantation, with or without cardioverter defibrillator, between 2004 and 2022. Inclusion criteria were: HF patients, with reduced LVEF and prolonged QRS intervals, submitted to treatment according to European recommendations

at the time of implantation and followed up at the Cardiology Department of Centro Hospitalar e Universitário de Coimbra for a minimum period of six months. Patients without adequate transthoracic echocardiographic LVESV records immediately before and/or at six-month of follow-up; who had a pacing/defibrillation system upgrade; loss of follow-up; lack of data regarding mortality, HF hospitalisations, NYHA functional class classification and cardiac transplantation, were excluded.

Statistical analysis

"IBM Statistical Package for the Social Sciences, Statistics version 26" (SPSS inc., Chicago IL., USA) was used for computation. Quantitative variables are summarised as means ± standard deviation and qualitative variables as frequencies and percentages. Continuous variables were tested for normality using the Kolmogorov-Smirnov or Shapiro-Wilk test, as appropriate. Missing patient-level covariates were assumed to be missing and no imputation was performed.

Baseline characteristics population, at pre-implantation and six-month follow-up after CRT, were tested. For qualitative variables, we used the Pearson's Chi-squared test. If statistical differences were detected between the groups, we conducted a proportions multiple comparison by customized tables with *p*-value adjusted to the Bonferroni correction. For quantitative variables with normal distribution and variance homogeneity, we performed the One-way ANOVA method. If statistical differences were detected between the groups, we conducted a Bonferroni Post-hoc test. For quantitative variables with non-normal distribution or non-homogeneity of variance, we used the Kruskal-Walli test. If statistical differences were detected between the groups, we conducted a Multiple Pairwise-comparison test with *p*-value adjusted to the Bonferroni correction.

Composite outcomes included all-cause and CV mortality, HF hospitalisations, NYHA functional class classification and cardiac transplantation, and a statistical analysis was performed using a graphical bar chart for a proportional evaluation between the data.

Cox proportional hazards regression model was performed to estimate time-to-event risk analysis. We computed hazard ratio (HR), including analysis regarding the effect of different types of response on all-cause mortality and, after adjustment of possible confounders, on HF hospital admissions risks during follow-up.

Independent predictors of HF progression despite CRT were tested and compared between the Pr and those who showed some degree of response (NPr and R). For qualitative variables, we used the Pearson's Chi-squared test. For quantitative variables with normal

distribution and variance homogeneity, we used the Independent Samples T test. For quantitative variables with non-normal distribution or non-homogeneity of variance, we used the Mann Whitney U test. We completed the analysis with a logistic regression model to compute odds ratios (OR) and determine the presence of possible predictors of HF progression.

A *p*-value <0.05 was considered statistically significant.

Results

1) Clinical characteristics of the population

A total of 207 patients, who underwent successful CRT implantation, were included. Baseline characteristics are described in **Table 1**. The population was predominantly male (72.0%), with a mean age of 62.3 ± 11.7 years. Regarding HF etiology, 32.4% had ischemic cardiomyopathy, with R displaying the lowest prevalence, although statistically non-significant. Over two thirds of the sample were implanted with a defibrillator. Regarding associated comorbidities, there were no significant differences between the three groups. Considering HF pharmacological treatment, no statistical differences were demonstrated, except regarding digoxin, which was significantly more prescribed in the Pr group (with *p*=0.002; Pr vs R *p*=0.007; Pr vs NPr *p*=0.012). Additionally, R had higher prevalence of left bundle branch block (R 84.0% vs Pr 79.4% vs NPr 68.2%, with p=0.260). The mean QRS duration at pre-implantation was 151.6 ± 32.3 ms, with Pr displaying the shortest interval, although differences in QRS width between the groups were not statistically significant.

2) Comparison of clinical, functional and echocardiographic characteristics between pre-implantation and six-month follow-up after CRT

Comparisons between data at pre-implantation and at six-month of follow-up are presented in **Table 2.**

Regarding pre-implantation data, 21.6%, 67.5% and 10.8% of patients were in NYHA functional class II, III and IV, respectively. The Pr group featured the worst functional class at baseline. Mean LVEF was 26.7 ± 7.9%.

At the six-month assessment, 117 (56.5%) showed a decrease in LVESV ≥ 15% (R), 58 (28.0%) had worsening of their index volume (Pr) and 32 (15.5%) demonstrated stabilisation (NPr). The majority of patients improved their clinical, functional and echocardiographic status after CRT. The magnitude of this improvement was greater in the R group, nevertheless the NPr (NYHA class at baseline 2.7 ± 0.5 to 2.1 ± 0.8 at six-month follow-up) also showed a statistically significant betterment in functional response after CRT device implantation in comparison to the Pr (NYHA class at baseline 3.0 ± 0.7 to 2.6 ± 0.8 at six-month follow-up), as shown in **Figure 1**.

3) Survival analysis

Comparisons of the composite outcomes between groups are featured in **Figure 2**.

During follow-up, 63 (30.4%) patients died, with 25 (14.0%) due to CV cause. Sixty-nine (33.3%) patients were hospitalised due to decompensated HF and 17 (8.2%) ended up needing cardiac transplantation. We registered higher overall mortality in the Pr, with the NPr group demonstrating a statistically non-significant lower mortality (Pr 48.3% vs NPr 31.2% vs R 21.4%; with p=0.001, Pr vs R p=0.001). Considering CV death, a similar correlation was identified, with the Pr group showing the highest CV mortality rate, and the NPr with a statistically non-significant better rate (Pr 36.7% vs NPr 13.3% vs R 3.0%; with p<0.001, Pr vs R p<0.001). HF hospitalisations rate were different between groups; however, the Pr showed a statistically non-significant higher prevalence compared to the NPr, with the R group featuring the lowest rate (Pr 50.0% vs NPr 37.5% vs R 23.9%; with p=0.002, Pr vs R p=0.002). The Pr group required more cardiac transplantations compared to the NPr, although statistically non-significantly, and to the R (Pr 19.0% vs NPr 12.5% vs R 1.7%; with p<0.001, Pr vs R p<0.001, NPr vs R=0.018).

Cox proportional hazards regressions curves are presented in **Figures 3 and 4**.

According to time-to-event risk analysis, survival rate differed significantly between the response groups, mainly due to significant lower all-cause mortality risk in the R group compared to the other groups. Pr demonstrated a two-fold increase in all-cause mortality risk compared to the R (HR: 2.595, 95% confidence interval (CI) 1.512-4.452, p<0.001), with NPr displaying an intermediate risk, with lesser extent ratio (HR: 2.101, 95% CI 1.003-4.398, p=0.049). After adjustment of possible confounders (including digoxin use, age, and gender), the category of CRT's response remained as an independent predictor of HF hospitalisations event risk, with statistical differences between the groups, mainly due to significant lower HF-related hospital admissions risk in the R group compared to the other groups. The R showed a two-fold decrease of HF hospitalisations risk when compared to the Pr (HR: Pr vs R = 2.641, 95% CI 1.540-4.530, p<0.001), and to the NPr group, although the latter to a lesser extent (HR: NPr vs R = 2.536, 95% CI 1.262-5.096, p=0.009).

4) Predictors of negative response to CRT:

Fifty-eight (28.0%) patients demonstrated HF progression despite treatment, termed the Pr. Regarding pre-implantation characteristics, no statistical differences were found between the "Pr" vs "NPr and R", except for a higher prevalence of NYHA class IV (p=0.002) and further chronic treatment with digoxin (p=0.001) and with ACEi/ARB (p=0.026). Pr had significantly

lower heart rate (mean rank: 70.3 beats per minute (bpm)) compared to the other groups (mean rank: 88.6 bpm, *p*=0.034).

Multivariate analysis targeting all possible factors associated with major adverse cardiovascular events was performed, focused on the covariates mentioned above with p-value <0.05 as well as the most clinically relevant to the study. They were included in a logistic regression as shown in **Table 3**. The multivariate analysis showed ischemic cardiomyopathy (OR 6.463, 95% CI 1.719-24.292, *p*=0.006), chronic renal disease (OR 4.686, 95% CI 1.120-19.607, *p*=0.034) and NYHA class IV at baseline (OR 4.580, 95% CI 1.498-14.001, *p*=0.008) as predictors of HF progression during CRT. Older patients had a slightly lower odd of progression (OR 0.934, 95% CI 0.883-0.988, *p*=0.018).

Tables and Figures

Table 1: Clinical characteristics of the population

	Pr	NPr	R	Pr vs NPr (p)	Pr vs R (p)	NPr vs R (p)	Pr vs NPr vs R (p)
Age, years, mean ± SD	61.0 ± 12.8	61.4 ± 12.6	63.1 ± 10.8	ns	ns	ns	0.500
Male gender, n (%)	45 (77.6)	25 (78.1)	79 (67.5)	ns	ns	ns	0.265
Ischemic cardiomyopathy, n (%)	19 (32.7)	15 (46.9)	33 (28.2)	ns	ns	ns	0.135
CRT-D, n (%)	45 (77.6)	26 (81.3)	93 (79.5)	ns	ns	ns	0.914
Diabetes, n (%)	15 (26.3)	9 (28.1)	39 (33.6)	ns	ns	ns	0.583
Arterial hypertension, n (%)	22 (53.7)	18 (75.0)	47 (60.3)	ns	ns	ns	0.232
Chronic renal disease, n (%)	12 (32.4)	10 (43.5)	21 (29.2)	ns	ns	ns	0.444
Dyslipidaemia, n (%)	26 (61.9)	19 (79.2)	52 (65.0)	ns	ns	ns	0.332
Beta-blocker, n (%)	52 (89.7)	25 (83.3)	98 (86.0)	ns	ns	ns	0.676
ACEi/ARB or ARNi, n (%)	56 (96.6)	28 (93.3)	105 (92.1)	ns	ns	ns	0.531
ACEi/ARB, n (%)	52 (89.7)	22 (73.3)	87 (76.3)	ns	ns	ns	0.078
ARNi, n (%)	4 (6.9)	6 (20.0)	18 (15.8)	ns	ns	ns	0.161
Spironolactone, n (%)	41 (70.7)	21 (70.0)	81 (71.1)	ns	ns	ns	0.993
Statins, n (%)	25 (55.6)	20 (74.1)	70 (69.3)	ns	ns	ns	0.176
ASA, n (%)	19 (41.3)	10 (37.0)	31 (30.4)	ns	ns	ns	0.410
Furosemide, n (%)	44 (95.7)	24 (88.9)	92 (92.0)	ns	ns	ns	0.549
Digoxin, n (%)	30 (51.7)	6 (20.0)	32 (28.1)	**0.012**	**0.007**	ns	**0.002**
Ivabradine, n (%)	5 (11.4)	5 (19.2)	7 (7.3)	ns	ns	ns	0.196
Sinus Rhythm, n (%)	52 (89.7)	25 (78.1)	103 (88.0)	ns	ns	ns	0.260
Heart rate, bpm, mean ± SD	64.6 ± 11.3	65.8 ± 8.6	70.5 ± 17.0	ns	ns	ns	0.064
LBBB, n (%)	27 (79.4)	15 (68.2)	63 (84.0)	ns	ns	ns	0.260
QRS duration, ms, mean ± SD	146.9 ± 32.8	148.1 ± 30.7	154.8 ± 32.5	ns	ns	ns	0.218
Follow-up, months, mean ± SD	51.9 ± 33.7	44.0 ± 24.9	58.2 ± 34.2	ns	ns	ns	0.088

ASA: acetylsalicylic acid; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNi: angiotensin receptor/neprilysin inhibitor; CRT-D: cardiac resynchronization therapy with defibrillator; LBBB: left bundle branch block; ms: milliseconds; NPr: Non-Progressors; n: number of cases; %: percentage; p: *p*-value; Pr: Progressors; R: Responders; SD: standard deviation; ns: statistically non-significant; vs: versus.

Table 2: Comparison of clinical, functional and echocardiographic characteristics between pre-implantation and six-month follow-up after CRT

	Pr	NPr	R	Pr vs NPr (p)	Pr vs R (p)	NPr vs R (p)	Pr vs NPr vs R (p)
Nº HF hospitalisations (year-earlier before CRT), mean ± SD	0.5 ± 0.8	0.5 ± 1.0	0.6 ± 1.1	ns	ns	ns	0.732
NYHA class IV (pre-implantation CRT), n (%)	13 (23.2)	1 (3.6)	7 (6.4)	ns	**0.005**	ns	**0.002**
NYHA class III (6-month after CRT), n (%)	24 (46.2)	5 (18.5)	25 (24.5)	**0.047**	**0.019**	ns	**0.008**
LVEF (pre-implantation CRT), %, mean ± SD	27.2 ± 9.0	28.1 ± 8.6	26.0 ± 7.1	ns	ns	ns	0.466
LVEF (6-month after CRT), %, mean ± SD	26.1 ± 9.0	31.1 ± 8.9	39.8 ± 10.8	ns	**<0.001**	**0.001**	**<0.001**
LVESV (pre-implantation CRT), mL, mean ± SD	173.1 ± 84.8	180.8 ± 114.7	174.2 ± 73.1	ns	ns	ns	0.978
LVESV (6-month after CRT), mL, mean ± SD	209.9 ± 90.7	167.9 ± 104.1	98.8 ± 51.3	ns	**<0.001**	**<0.001**	**<0.001**
LVEDV (pre-implantation CRT), mL, mean ± SD	234.0 ± 100.1	240.4 ± 128.4	231.7 ± 84.0	ns	ns	ns	0.994
LVEDV (6-month after CRT), mL, mean ± SD	276.1 ± 107.7	235.3 ± 129.1	160.7 ± 65.1	ns	**<0.001**	**0.001**	**<0.001**
MR ≥ grade 3 (pre-implantation CRT), n (%)	9 (25.7)	2 (8.7)	18 (26.9)	ns	ns	ns	0.188
MR ≥ grade 3 (6-month after CRT), n (%)	17 (34.0)	4 (16.7)	5 (5.3)	ns	**<0.001**	ns	**<0.001**
sPAP (pre-implantation CRT), mmHg, mean ± SD	37.5 ± 17.1	37.4 ± 14.0	33.1 ± 16.0	ns	ns	ns	0.897
sPAP (6-month after CRT), mmHg, mean ± SD	43.5 ± 13.2	37.7 ± 22.5	31.0 ± 6.9	ns	**0.002**	ns	**0.003**
Δ LVESV, mL, mean ± SD	(-0.3) ± 0.6	0.1 ± 0.0	0.4 ± 0.2	**0.002**	**<0.001**	**<0.001**	**<0.001**

CRT: cardiac resynchronization therapy; HF: heart failure; LVEF: left ventricle ejection fraction; LVEDV: left ventricle end-diastolic volume; LVESD: left ventricle end-systolic volume; mL: milliliter; mmHg: millimeter of mercury; MR: mitral regurgitation (grade 0 - none; grade 1 - mild; grade 2 - moderate; grade 3 - moderate to severe; grade 4 - severe); NPr: Non-Progressors; NYHA: New York Heart Association; Nº: number of; n: number of cases; %: percentage; Pr: Progressors; p: *p*-value; R: Responders; SD: standard deviation; ns: statistically non-significant; sPAP: systolic pulmonary artery pressure; vs: versus; Δ: variation;

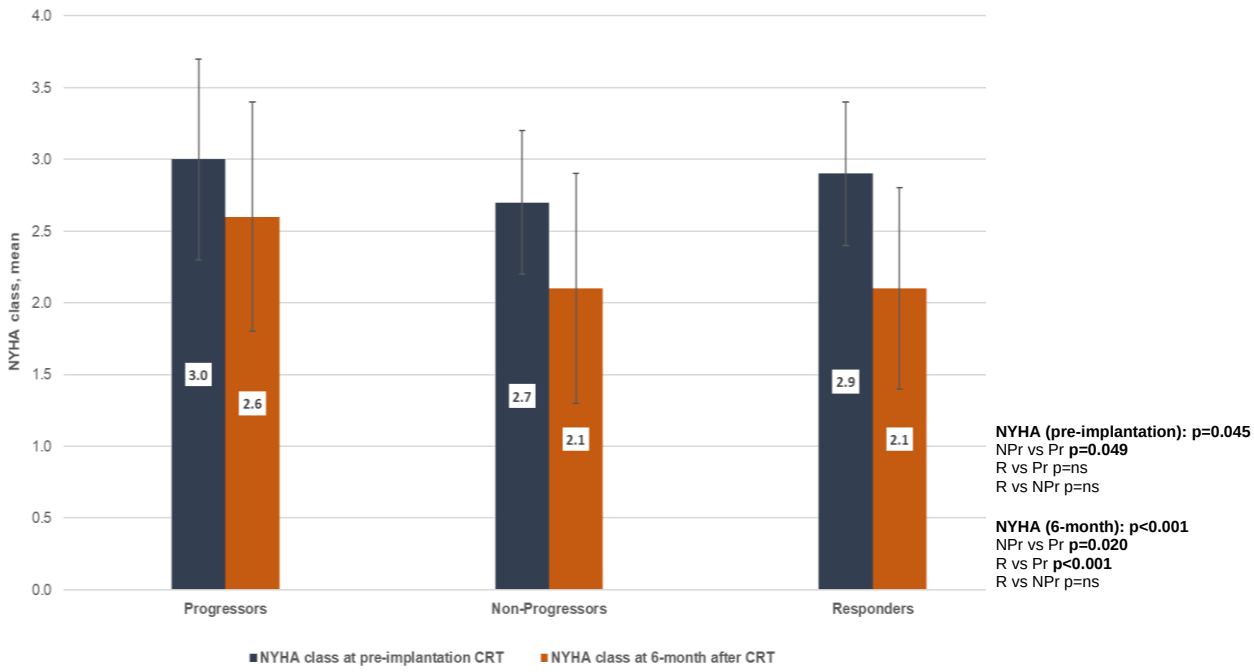

Figure 1: Comparison of NYHA functional class response at pre-implantation and six-month follow-up after CRT between groups. CRT: cardiac resynchronization therapy; NYHA: New York Heart Association; NPr: Non-Progressors; Pr: Progressors; p: *p*-value; R: Responders; ns: statistically non-significant; vs: versus.

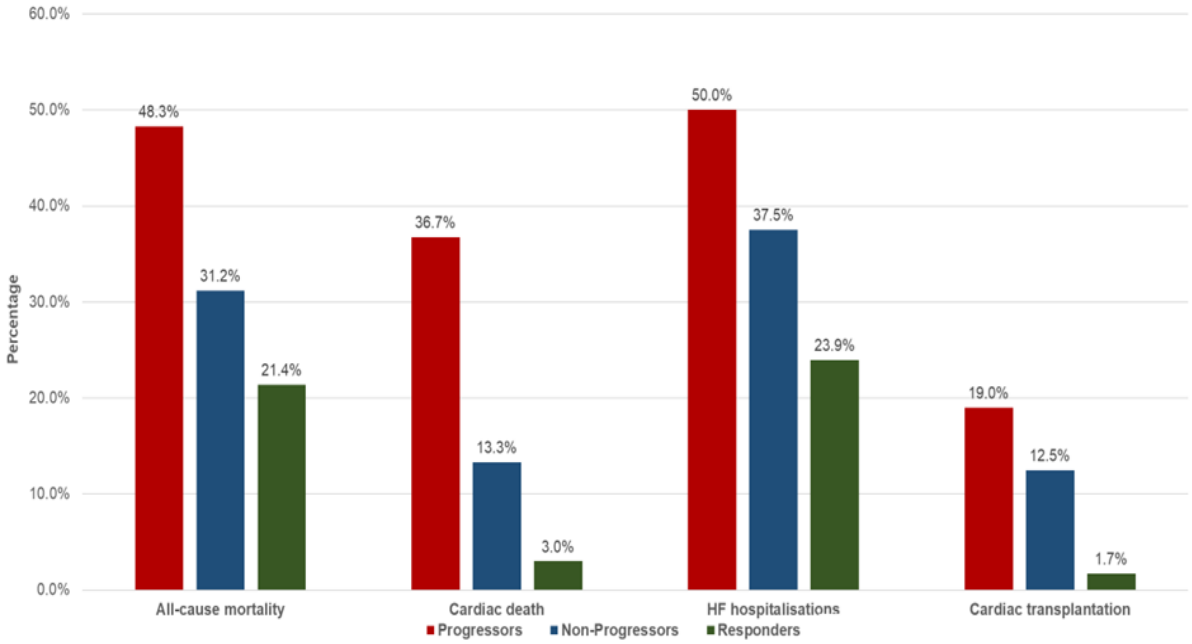

Figure 2: Comparisons of the composite outcomes between groups. HF: heart failure.

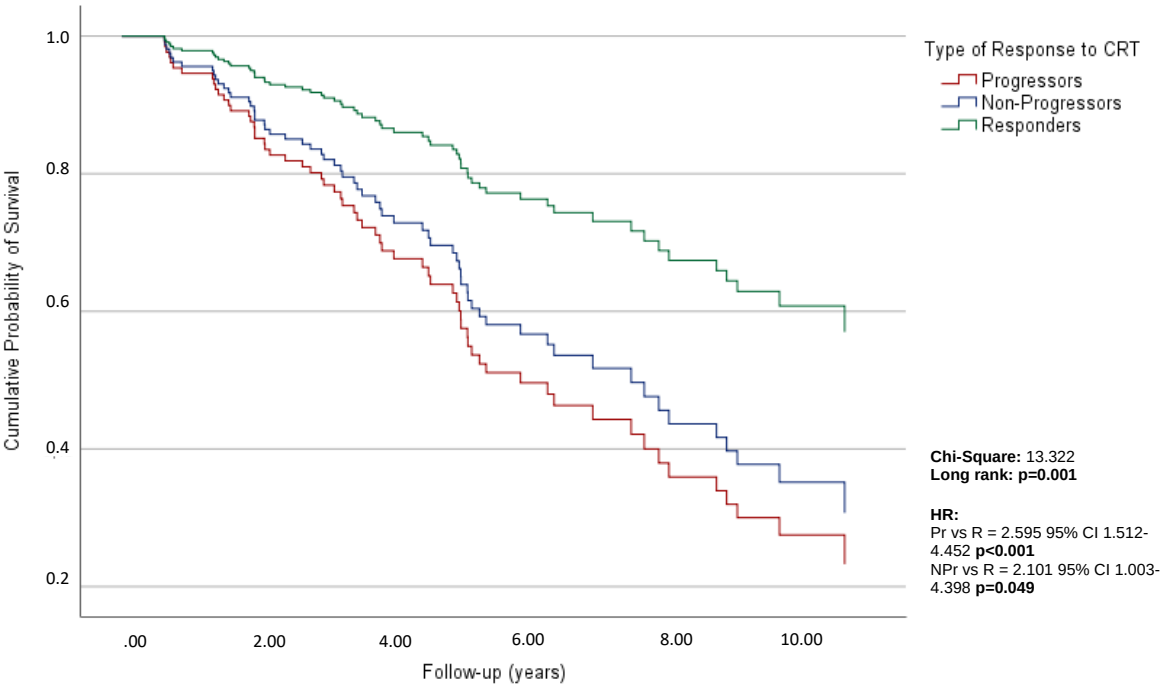

Figure 3: Cox proportional hazards regression for survival curve of all-cause mortality risk analysis depending on the response to CRT. CRT: cardiac resynchronization therapy; CI: confidence interval; HR: hazard ratio; NPr: Non-Progressors; Pr: Progressors; p: *p*-value; R: Responders; vs: versus.

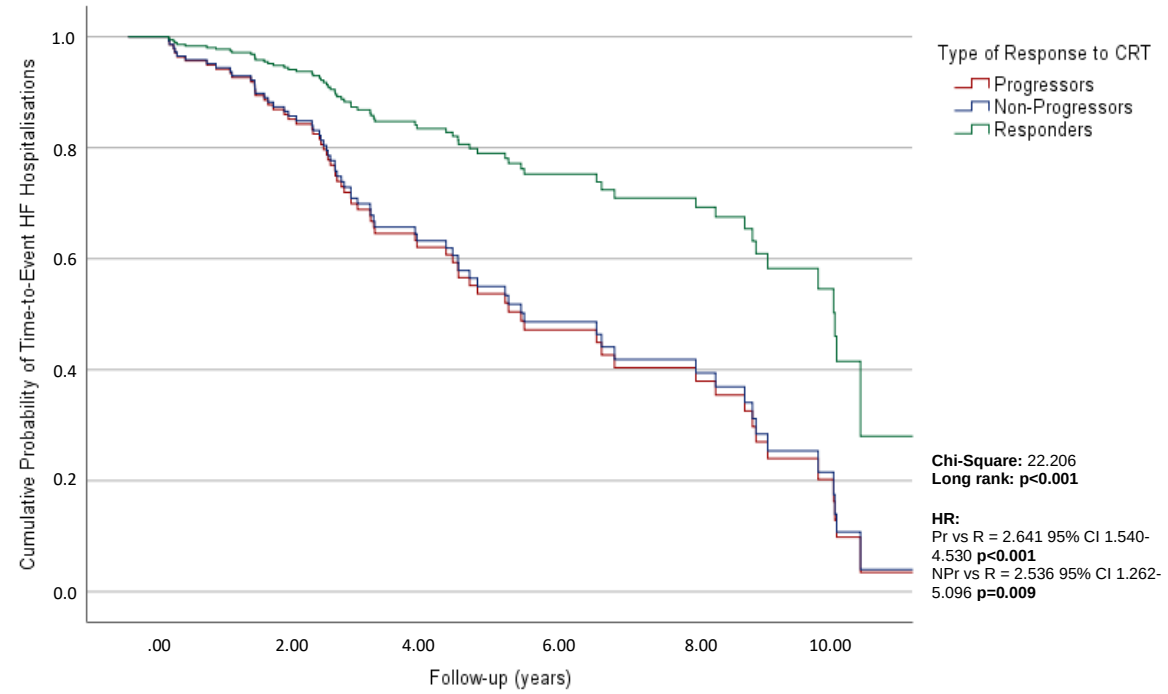

Figure 4: Cox proportional hazards regression curve for time-to-event HF hospitalisations risk analysis depending on the response to CRT. CRT: cardiac resynchronization therapy; CI: confidence interval; HR: hazard ratio; NPr: Non-Progressors; Pr: Progressors; p: *p*-value; R: Responders; vs: versus.

Table 3: Multivariate analysis of predictors of HF progression despite CRT

Characteristics	Logistic Regression		
	OR	95% CI	p
Age, years	0.934	0.883 - 0.988	**0.018**
Male gender	1.905	0.103 - 2.687	0.439
Ischemic cardiomyopathy	6.463	1.719 - 24.292	**0.006**
Diabetes	0.352	0.090 - 1.367	0.131
Arterial hypertension	1.046	0.393 - 2.779	0.928
Dyslipidaemia	1.007	0.381 - 2.660	0.988
Chronic renal disease	4.686	1.120 - 19.607	**0.034**
ACEi/ARB	2.970	0.812 - 10.859	0.100
Digoxin	1.790	0.352 - 9.110	0.483
Heart rate, bpm	0.988	0.955 - 1.022	0.492
Non-LBBB	1.585	0.274 - 1.458	0.282
NYHA class IV (pre-implantation CRT)	4.580	1.498 - 14.001	**0.008**
LVESV (pre-implantation CRT), mL	1.000	0.991 - 1.009	0.977

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; bpm beats per minute; CRT: cardiac resynchronization therapy; CI: confidence interval; LBBB: left bundle branch block left; LVESD: left ventricle end-systolic volume; mL: milliliter; NYHA: New York Heart Association; OR: odds ratio; p: *p*-value.

Discussion

Our study further validates the recent concept that patients without improvement of LV geometry, but who stabilise after CRT, are not true “non-responders”, reinforcing the need for an update of the previous response definition that dichotomised patients as “responders” vs “non-responders” to treatment. The newfound phenotype, the NPr, who do not reach a reduction in LVESV ≥ 15%, nevertheless exhibits remodeling stabilisation during treatment, cannot continue to be pooled with those of evident worsen LV status, the Pr. [28–31] This situation is particularly worrisome, since it is erroneous to strip away CRT’s ability to blunt the remodeling process as a positive result, especially in light of the progressive nature of HF. [32] The present study was able to demonstrate that CRT is capable of providing better outcome trajectories to this subset of patients compared to the remaining “non-responders”. Following this concept, the main findings of our work are: 1) the demonstration that improved outcomes observed in CRT parallel its impact on LV geometry, with a continuum in the outcomes from Pr, to NPr, and finally R. Of note, the NPr group demonstrated, although non-significantly, improved outcomes of all-cause and CV mortality, HF hospitalisations and need for cardiac transplantation compared to the Pr; 2) a continuum of functional class improvement, with statistical significance, after CRT from the NPr to the Pr; 3) the proof that CRT helps to slow down HF progression, since curves of all-cause mortality and HF-related hospitalisations risks began to separate within a few months after implantation, with noticeable greater rates from the R group, remaining throughout the follow-up time; and finally 4) based on the hazard ratio and time-to-event risk analysis, reverse remodeling with LVESV reduction ≥15%, guarantees a significantly better long-term prognosis with improved survival and less HF-related hospitalisations risk, since the Pr and NPr, although the latter to a lesser extent, are associated with roughly similar two-fold risk increase in both rates, when compared to the R. We postulate that the differences between the outcomes rate ratio and hazard ratio is possibly explained by the progressive nature of the disease and therefore the time variable influence. The instantaneous risk of these events changes over time, especially since CRT’s effects become limited when NPr develop more rapidly into further advanced and irreversible remodeling phases or with more extracardiac comorbidities and pharmacological burden, which might trigger decompensated states leading to higher hospitalisation risk and precipitate mortality, including of noncardiac causes.

New research suggests increased survival benefits of the NPr compared to the Pr, going further to link them with a similar prognosis of those classified as R. [27] Around 2014, Steffel and Ruschtizka [33] resurface the issue of an absence of uniformed criteria, proposing a modified classification, introducing the term NPr. This new subset of patients was previously included

has “non-responders” (“failure to improve”), although they experienced minimal reverse in remodeling indices after CRT. They were thought to have improved outcomes and survival in comparison to those who continued to remodel even with a functional device (Pr). [32] In 2020, a statement from various European Society of Cardiology Associations, Heart Failure Association, European Heart Rhythm Association and European Association of Cardiovascular Imaging, focused solely on optimising CRT and its potential treatment effects, recommended abandoning the term non-response, replacing it with the concept of disease modification. [34] In concordance with our results, Rickard et al [32] concluded that, although with a different criteria of echocardiographic response (change in LVEF), NPr displayed improved medium-term outcomes, nevertheless comparable long-term outcomes with the Pr. This analysis is quite meaningful, since many other studies are often limited with shorter follow-ups, not allowing an extrapolation for a longer-term evaluation. As previously mentioned, such analysis is explained by CRT’s inability to reverse once NPr reach irreversible LV remodeling and, therefore inevitable greater clinical and treatment burden. Furthermore, similar to our study, the percentage of patients falling into the NPr were unexpectedly higher than anticipated, reenforcing the idea of CRT's response success rate of roughly 60% being a clear underestimation. Gold et al [27], authors of a randomized double-blind trial on CRT in NYHA Class I and II HF patients, reported that patients who stabilised early after CRT had improved long-term outcomes of overall mortality and HF hospitalisations. [35] Chung et al [36], who collected data from five prospective CRT cohort clinical trials, with a six-month LVESV change as endpoint, on patients with NYHA class III to IV, reported improved outcomes of mortality by any cause and HF hospital admissions within the NPr compared to the Pr. Our study reached similar outcome trajectories with patients between NYHA class II-IV, mostly class III.

These findings further support that dichotomising CRT's response in “responders” vs “non-responders”, might be insufficient, underestimating CRT benefits within an intermediate forgotten category, the NPr, suggesting a modification of the current conventional classification of “non-responders”, which better reflect its potential. [37]

In our study, the criteria used for patient’s stratification was focused on a six-month echocardiographic indice of LVESV range, rather than another echocardiographic parameter such as LVEF, or clinical status change. The fact that there is a widespread concept of response, with endless definitions and little agreement between measures of symptomatic improvement to the arbitrary cut-offs of different echocardiographic criteria, in addition to potential confounders, it leads to a lack of consensus regarding how to measure and what magnitude of change constitutes response. [33,38,39] Therefore, the ideal endpoint to represent CRT's response is still in debate. Nevertheless, we note a discrepancy between clinical and echocardiographic parameters, with much improved response rates and greater reproducibility

when patients are divided by clinical parameters. [40,41] However, most randomized CRT clinical trials assess an echocardiographic measure as baseline, preferably LVESV instead of LVEF change. It is known that LVESV is more sensitive when assessing the degree of ventricular remodeling, while LVEF is a stronger indicator of contractility. Hsu et al [42] analysed data from the "Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronization Therapy", which confirmed LVESV as a stronger predictor of response to CRT, suggesting LV reverse remodeling as the key factor in identifying who will develop the best response. Interestingly enough, in our study we were able to prove the impact improvement of LVESV has on long-term prognosis, demonstrating a statistically significant connection between positive reverse remodeling and CRT's success rate in terms of outcomes and time-varying risk analysis. In addition, we managed to connect, with significance, improvement of LVESV value with betterment of a more subjective clinical criteria such as NYHA functional class, both correlated with greater response rates.

Finally, to further understand the potential effects of CRT, we evaluated unfavorable factors that impact the response, thus leading to HF progression despite CRT. Our goal was not only to maximize the results, but also to identify cases in which treatment will be futile, independently of the reverse remodeling potential, demanding better and more suitable alternatives. We concluded that ischemic cardiomyopathy, chronic renal disease and NYHA class IV at baseline are statistically significant predictors of HF progression. Ischemic cardiomyopathy is already known as a predictor of negative response with reduced capacities for reverse remodeling, mainly related to the smaller baseline LV volumes and due to the restrictive nature of the fibrotic scaring within the myocardium, [5,27,43] all in agreement with findings from other CRT's studies. [44–46] Identifying factors associated with irreversible disease regarding the potential of reverse remodeling, will allow better patient selection and exclusion of those who will not benefit from CRT.[27]

Limitations

As a single-center study design, despite covering a large period of patient selection, it does not include a very large sample size. Therefore, including other centers with similar inclusion criteria could increase accuracy of our study.

Secondly, this was a retrospective observational study with patients submitted to CRT, irrespective of their baseline characteristics of heart rhythm, comorbidities and HF etiology. Also, there might be unidentified confounders, despite our best efforts to analyse them.

Thirdly, the exclusive use of echocardiographic parameter LVESV to stratify CRT's response might be restrictive. Latest studies in this field report other equally relevant indicators to be considered, apart from echocardiographic evaluation of reverse remodeling, that have shown to influence CRT's success rate.

Other limitations include the absence of a "non-CRT" control group and the exclusion of patients with pacing/defibrillation system upgrade, which causes an underrepresentation of the real-world CRT's population.

Conclusions

In HF patients submitted to CRT, Non-Progressors demonstrated non-significantly better outcomes of all-cause and CV mortality, HF hospital admissions and need for cardiac transplantations, and significantly improvement in functional class response, compared to the Progressors. Considering hazard ratio analysis of all-cause mortality and HF hospitalisations risk, patients with HF stabilisation had similar results, although to a lesser extent, to the ones that deteriorated, with an approximated two-fold increased risk in both rates when compared to the Responders. Hence, reverse LV remodeling (reduction in LVESV <15%), and not only stabilisation, seems to be required for improved long-term prognosis with fewer time-to-event risks associated.

Patients with ischemic cardiomyopathy, chronic kidney disease and with a more advanced functional class at baseline are at a higher risk for a negative response to CRT. These patients have higher risk of HF progression and therefore to worse prognosis. This emphasis the importance of careful evaluation of patients before implantation, in order to avoid futility and associated costs.

Acknowledgments

First and foremost, I would like to express my gratitude to my primary supervisor, Professora Doutora Natália Sofia Cláudio António, who guided me throughout this project. Additionally, I wish to acknowledge the assistance and advice provided by Doutora Patrícia Marques Alves, Doutora Marta Sofia de Jesus Madeira e Doutora Ana Rita Morgado Gomes. I would also like to show my appreciation to Doutor Diogo Almeida Fernandes, who offered valuable statistics which helped finalise the project.

A heartfelt acknowledgement to Professor Doutor Lino Manuel Martins Gonçalves, Director of the Cardiology Department of Centro Hospitalar e Universitário de Coimbra, for allowing us to pursue with our original vision and providing all the resources. Equally, to the Ethics Committee of Centro Hospitalar e Universitário de Coimbra for the project's approval.

Finally, I would like to thank my parents, big sister, nephew and friends for the constant support and words of encouragement. Without you, I wouldn't be where I am today.

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