Original Article

De Novo Versus Upgrade Cardiac Resynchronization Therapy in Patients with Heart Failure: A Cohort Study

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Abstract

Background: Cardiac resynchronization therapy (CRT) is beneficial for patients with heart failure (HF) who have left bundle branch block. However, the benefits of CRT in patients with prior cardiac stimulation remain uncertain.

Objective: Compare short-term mortality between upgrade and de novo CRT implantation.

Methods: This prospective cohort study included patients with HF indicated for CRT with left ventricular ejection fraction (LVEF) below 35%. Overall survival was assessed using the Kaplan–Meier method, and multivariate analysis was performed using a Cox regression model.

Results: A total of 412 patients were evaluated, with a mean follow-up of 59 ± 8 months. Of these, 104 patients were in the upgrade group, while 308 patients were included in the de novo group. Chagas disease was the most prevalent cause of HF, accounting for 148 cases (36%). While the de novo group progressed with an increase in LVEF (from 25% ± 6.7% to 28% ± 16.3%, p = 0.005), patients who underwent upgrade did not show a statistically significant difference in LVEF at 6 months (from 27.5% ± 6.9% to 27.5% ± 15.5%, p = 0.6). Overall mortality at 1 year was 122 cases (29.6%). In multivariate analysis, only LVEF and CRT upgrade remained independently associated with the outcome (hazard ratio: 0.93, confidence interval: 0.90 to 0.97, p = 0.001 and hazard ratio: 2.90, confidence interval: 1.21 to 7.10, p = 0.002, respectively).

Conclusion: In this population with HF, the upgrade group was associated with higher 1-year mortality when compared with the de novo group.

Keywords: Chagas Disease; Implantable Defibrillators; Heart Failure; Chagas Cardiomyopathy.

Introduction

Randomized clinical trials support the clinical efficacy and safety of cardiac resynchronization therapy (CRT) in patients with moderate or severe heart failure (HF) and ventricular dyssynchrony.[1,2] Guidelines from international cardiology societies provide strong recommendations for CRT, especially in symptomatic patients with left bundle branch block (LBBB) and QRS duration > 150 ms.[3] Nonetheless, important questions remain regarding the clinical application of this therapy in specific populations.

Upgrading from a conventional pacemaker to CRT has become increasingly common in patients with HF, since right ventricular pacing can worsen left ventricular function.[4] Nonetheless, concerns remain regarding this approach, as it is supported by small-scale observational studies. Accordingly, recent evidence has suggested that clinical response and survival are impaired in patients undergoing CRT upgrade in comparison with de novo therapy.[5,6]

Therefore, the aim of this study was to compare short-term mortality between upgrade and de novo CRT implantation in a population with HF, in which Chagas disease is endemic.

Methods

Population

This prospective cohort study was conducted between May 2017 and September 2023, including consecutive patients over 18 years of age, followed at the HF unit of a tertiary hospital in Bahia, Brazil. The indication for CRT was based on the following criteria: patients over 18 years of age, receiving adequate medical treatment, classified as New York Heart Association (NYHA) functional class II to IV, left ventricular ejection fraction (LVEF) below 35%, and QRS duration > 150 ms or 120 to 150 ms with LBBB. Patients

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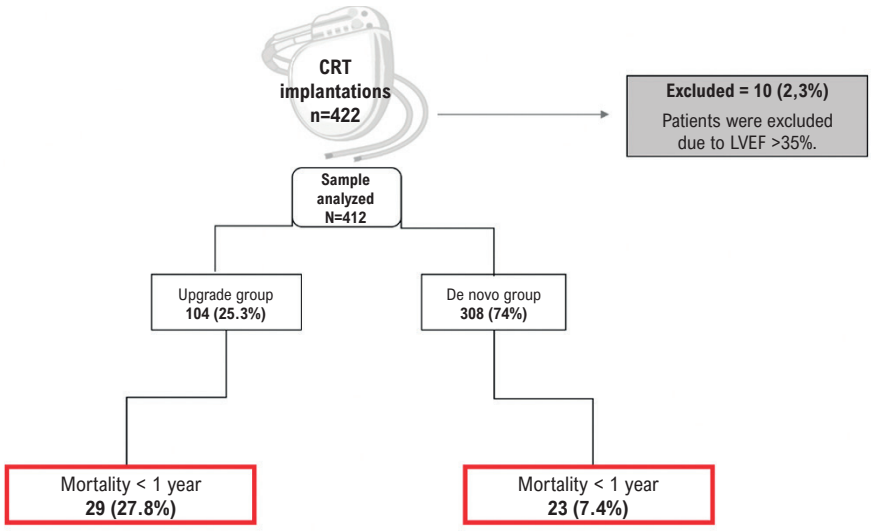
Manuscript received February 12, 2024, revised manuscript July 04, 2024, accepted July 27, 2024
Editor responsible for the review: Luis Beck-da-Silva

DOI: https://doi.org/10.36660/abchf.20240008i

Central Illustration: De Novo Versus Upgrade Cardiac Resynchronization Therapy in Patients with Heart Failure: A Cohort Study



ABC Heart Fail Cardiomyop. 2024; 4(2):e20240008

CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction.

with previously implanted pacemakers or implantable cardioverter-defibrillators who developed these criteria, with or without requiring continuous ventricular pacing, were also considered for CRT (upgrade group).

Demographic, laboratory, and echocardiographic data were collected at the time of hospitalization for the procedure. All patients were electively hospitalized for the procedure, and NYHA functional class was assessed at the time of hospitalization. LVEF was measured by transthoracic echocardiogram using the Simpson method at the time of CRT implantation and after 6 months. Atrial fibrillation was defined at the time of the procedure by baseline electrocardiogram. Chagas disease was confirmed by specific serological tests.

Patients were excluded if they had chronic systemic inflammatory disease, were undergoing treatment for malignant neoplasm, refused the procedure, or did not provide informed consent.

Follow-up and Outcomes

Patients were followed up by regular outpatient visits after hospital discharge. Echocardiography was performed 6 months after the procedure. Hospitalization for HF was assessed during follow-up. Patients with LVEF > 50% at 6 months were considered super-responders. Patients who did not return within 1 year after CRT implantation were contacted via telephone. Survival was assessed from the time of CRT implantation until all-cause mortality.

Ethical Considerations

The local ethics committee approved this study, and all procedures were performed in accordance with the Declaration of Helsinki.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. Normally distributed variables were described as means and standard deviations and compared using unpaired Student's t test. To compare the mean difference in LVEF after 6 months, the paired t test was performed. Nonparametric variables were described as medians and interquartile ranges and compared using the Mann–Whitney test. Categorical data were shown as absolute numbers and percentages of the total sample and compared using Fisher's exact test. Overall survival was calculated using the Kaplan–Meier method, and the log-rank test was used to compare survival curves. A p value < 0.05 was considered statistically significant. To identify variables that were independently predictive of overall mortality, a subsequent multivariate analysis was performed using the Cox regression model, including variables that had a predictive value of $p < 0.10$ in the univariate analysis of overall survival (log-rank test). Statistical Package for the Social Sciences (SPSS) version 20.0 was used to analyze all data.

Results

A total of 422 patients were evaluated for CRT implantation, and 10 of them were excluded due to LVEF

greater than 35% before the procedure (Central Illustration). Of the remaining 412 patients, Chagas disease was the most prevalent cause of HF, with 148 patients (36%), followed by ischemic cardiomyopathy, with 65 (15.7%) patients. There was no loss to follow-up for the main outcome, with a mean duration of 59 ± 8 months. There were 104 patients in the upgrade group, 86 (82.7%) who were upgraded from right ventricular pacing and 18 (17.3%) who had a previous implantable cardioverter defibrillator. The baseline demographic characteristics of the upgrade and de novo groups are displayed in Table 1. Chagas cardiomyopathy was more prevalent in patients in the upgrade group (76 [73%] versus 72 [23.3%], p < 0.001), whereas ischemic cardiomyopathy (9 [8.6%] versus 56 [18%], p = 0.008), myocarditis (2 [1.9%] versus 60 [19.5%], p < 0.001), idiopathic (5 [4.8%] versus 48 [15.6%], p = 0.004), and other etiologies (12 [11.7%] versus 78 [23.3%], p = 0.011) were more prevalent in the de novo group. Atrial fibrillation was more common in the upgrade group (36 [34.6%] versus 53 [17.2%], p = 0.006), and LVEF was lower in the de novo group (25% ± 9.0% versus 26% ± 7.1%, p = 0.038). Other demographic, clinical, and HF treatment characteristics were similar in both groups. Only 85 (20%) patients underwent CRT implantation without LBBB (induced or spontaneous). Among patients with Chagas cardiomyopathy, 72 (48.6%) had induced LBBB, 20 (13.5%) had spontaneous LBBB, and 52 (35.1%) had right bundle branch block.

Paired echocardiographic assessments (baseline and 6-month follow-up) were available in 303 (73.5%) patients. LVEF at 6 months increased after CRT from 25% ± 6.8% to 28% ± 16% (p = 0.02). Subgroup analysis showed that only the de novo group showed improved LVEF on the 6-month echocardiogram, from 25% ± 6.7% to 28% ± 16.3% (p = 0.005), whereas the upgrade group did not show improvement, from 27.5% ± 6.9% to 27.5% ± 15.5% (p = 0.6). Eighteen (4.3%) patients met echocardiographic criteria for super-responders after CRT, 16 (5.1%) in the de novo group and 2 (1.9%) in the upgrade group (p = 0.178). No patients underwent heart transplantation during the study period.

During follow-up, overall mortality occurred in 122 (29.6%) patients. Death was more frequent in patients in the upgrade group compared with those undergoing de novo CRT implantation (37 [35.6%] versus 85 [27.6%], respectively, p < 0.001 by the log-rank test), as illustrated in Figure 1. There were 8 in-hospital deaths, all directly associated with the procedure, 6 in the upgrade group and 2 in the de novo group. In the univariate analysis, baseline LVEF, idiopathic cardiomyopathy, Chagas disease, and CRT upgrade were associated with overall mortality during follow-up. In the multivariate model, only baseline LVEF and CRT upgrade remained independently associated with the outcome (hazard ratio: 0.93 [0.90 to 0.97], p = 0.001 and hazard ratio: 2.90 [1.21 to 7.10], p = 0.002, respectively), as shown in Table 2.

Table 1 – General characteristics

	Upgrade group	De novo group	p
	104 (25.3%)	308 (74.7%)	
Male sex, n (%)	61 (58.6%)	178 (57.8%)	0.878
Age, mean (±SD)	61 (±11)	60 (±12)	0.601
NYHA class II or III, n (%)	93 (89.4%)	274 (89%)	0.685
NYHA class IV, n (%)	11 (10.6%)	34 (11%)	0.677
Hypertension, n (%)	77 (74%)	228 (74%)	0.998
Diabetes, n (%)	38 (36.5%)	99 (32%)	0.420
Atrial fibrillation, n (%)	36 (34.6%)	53 (17.2%)	0.006
Prior myocardial infarction, n (%)	14 (13.4%)	64 (20.8%)	0.075
Prior ischemic stroke, n (%)	22 (21.1%)	51 (16.5%)	0.290
LVEF, mean (±SD)	26 (±6.9)	24 (±6.7)	0.005
LBBB, n (%)	93 (89.4%)	232 (76%)	0.002
Intraventricular block, n (%)	11 (10.6%)	76 (24%)	0.003
QRS ≥ 150 ms, n (%)	64 (61.6%)	190 (61.7%)	0.818
QRS duration, mean (±SD)	150 (±14)	152 (±19)	0.417
CRT-D, n (%)	83 (79.8%)	185 (60%)	<0.001
Glomerular filtration rate, mean (±SD)	63 (±24)	67 (±24)	0.111
MAGGIC score % at 1 year, mean (±SD)	16.4 (±9.8)	16.1 (±8.7)	0.740
Chagas cardiomyopathy, n (%)	76 (73%)	72 (23.3%)	<0.001
Ischemic cardiomyopathy, n (%)	9 (8.6%)	56 (18%)	0.008
Myocarditis, n (%)	2 (1.9%)	60 (19.5%)	<0.001
Idiopathic, n (%)	5 (4.8%)	48 (15.6%)	0.004
Other etiologies	12 (11.7%)	78 (23.3%)	0.011
ACEI, ARB, or ARNI, n (%)	93 (89.4%)	272 (88.3%)	0.754
Beta blocker, n (%)	92 (88.4%)	255 (82.8%)	0.139
Spironolactone, n (%)	85 (81.7%)	252 (81.8%)	0.994
Furosemide, n (%)	87 (83.6%)	243 (78.9%)	0.273
Furosemide, mean dose in mg (±SD)	55 (±51)	59 (±47)	0.253

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CRT-D: cardiac resynchronization therapy combined with cardioverter-defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SD: standard deviation.

Discussion

We have described a prospective cohort of patients with HF and indication for CRT, in which Chagas disease was the most frequent cause of cardiomyopathy. There was no loss to follow-up, and the use of evidence-based medical therapies was higher than in the majority of previous clinical trials with CRT.[7,8] Furthermore, the indication for CRT was consistent with guideline-based recommendations, as most patients had LBBB (induced or spontaneous) and QRS ≥ 150 ms.

Patients who underwent upgrade with CRT implantation had similar clinical, echocardiographic, and demographic characteristics compared to the de novo CRT group, differing in relation to etiology, presence of atrial fibrillation, and LVEF. Unlike previous studies comparing de novo versus upgrade CRT, we found no difference in QRS duration between the two groups.[5,9,10]

The general population was high risk, with a mean LVEF of 25%, and the majority of patients were in NYHA functional class III or IV. CRT was generally effective in improving systolic performance, with a significant increase in LVEF. This left ventricular remodeling occurred consistently in the de novo group, but not in the upgrade group. This result is in line with a published study that demonstrated higher rates of improvement in patients undergoing de novo CRT compared with those in the upgrade group.[5]

However, we observed high overall mortality, 29.6% at 1-year follow-up, mainly in the CRT upgrade group. In the univariate analysis, Chagas disease, idiopathic etiology, LVEF, and CRT upgrade were directly associated with overall 1-year mortality, whereas CRT upgrade and LVEF were the only variables independently associated with the outcome in the multivariate model. Reduced LVEF is directly related to the severity of HF, and its association with mortality was an expected finding. The elevated mortality rate in the upgrade group is consistent with the study by Vamos et al., which followed 552 CRT implantations, including 177 upgrade procedures, and found a 1.65-fold increase in mortality.[5] Similarly, the cohort by Beca et al. found a 2.86-fold increase in long-term mortality.[11] On the other hand, these data differ from the previously cited meta-analysis and the European CRT survey, which demonstrated that CRT upgrade was associated with a similar risk of all-cause mortality compared with de novo CRT.[9]

A few factors may justify this evidence. First, it has been suggested that CRT upgrade procedures are associated with an increase in perioperative complications. In fact, most in-hospital deaths occurred in the CRT upgrade group and were directly related to the procedure. Our sample size was not sufficient to test this hypothesis. Reoperations are generally more complex and may pose a higher risk of complications, with higher infection rates and longer procedure times related to venous access problems and difficulties in extracting old leads. Data comparing complication rates after upgrade to CRT versus de novo CRT are limited and inconsistent. In a large-scale European CRT survey of 11,088 patients with 2,396 (23.2%) upgrade procedures, overall perioperative complication rates were similar between groups.[12] In contrast, Cheung et al., using the United States national database, found a significantly higher rate of complications in patients with CRT upgrade compared to patients undergoing de novo CRT, with a 2-fold risk of in-hospital mortality.[6]

Another hypothesis is that patients in the upgrade group had more advanced heart disease and more comorbidities, and biventricular pacing may have been indicated too late. In our series, patients in the upgrade group had similar baseline characteristics regarding advanced HF when compared with patients in the de novo group. Finally,

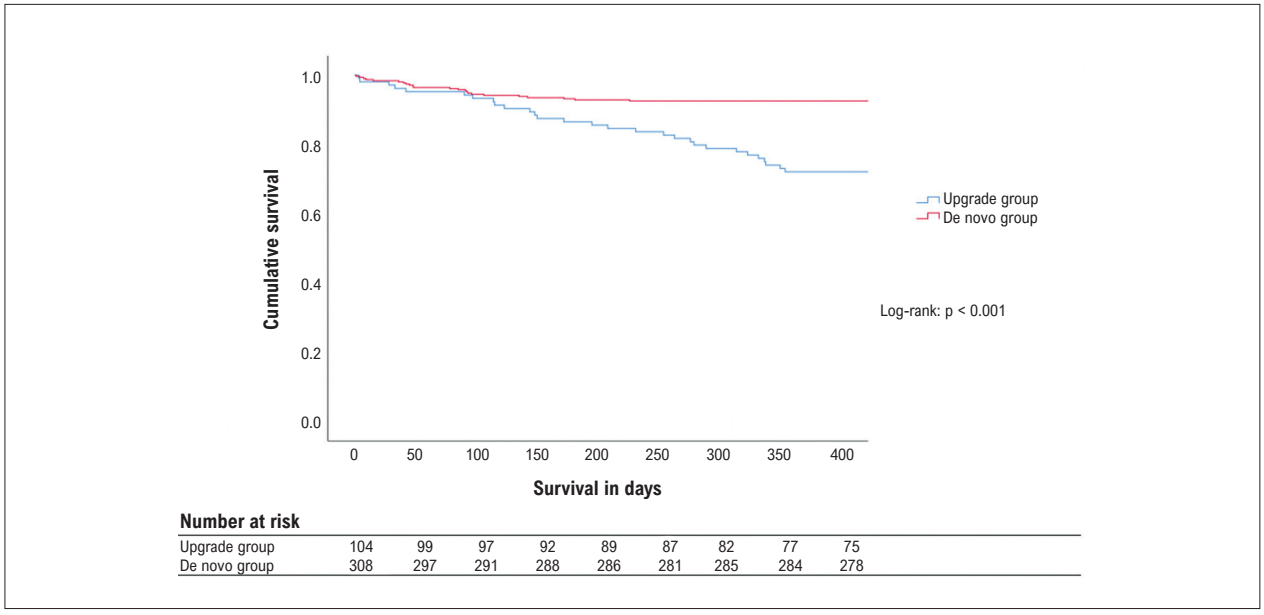


Figure 1 – *Kaplan–Meier survival curve of patients in the first year after upgrade and de novo cardiac resynchronization therapy implantation.*

Table 2 – Univariate and multivariate analysis of predictors of death from any cause using the Cox regression model

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age, years	1.01 (0.98 – 1.03)	0.594	-	-
Hypertension	0.75 (0.39 – 1.46)	0.403	-	-
NYHA class III or IV	0.85 (0.49 – 1.47)	0.555	-	-
LVEF (%)	0.95 (0.92 – 0.99)	0.017	0.93 (0.90 – 0.97)	0.001
Diabetes	1.03 (0.58 – 1.84)	0.920	-	-
Atrial fibrillation	0.7 (0.34 – 1.16)	0.139	-	-
CRT-D	1.32 (0.75 – 1.63)	0.210	-	-
Intraventricular block	0.94 (0.47 – 1.88)	0.868	-	-
Myocarditis	0.35 (0.11 – 1.08)	0.059	-	-
Idiopathic	0.13 (0.01 – 0.94)	0.007	0.21 (0.11 – 0.98)	0.070
Chagas disease	1.83 (1.40 – 2.40)	<0.001	2.11 (0.91 – 5.32)	0.106
Ischemic cardiomyopathy	0.80 (0.54 – 2.67)	0.649	-	-
Upgrade	2.67 (1.95 – 3.66)	< 0.001	2.90 (1.21 – 7.10)	0.002

CI: confidence interval; CRT-D: cardiac resynchronization therapy with defibrillator; HR: hazard ratio; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

especially in this HF population, Chagas disease may play a role in worsened patient survival. The pathophysiological and epidemiological characteristics of Chagas disease per se corroborate the adverse outcomes. Patients with HF due to Chagas cardiomyopathy have worse prognosis compared to other etiologies, with a higher incidence of death due to HF progression and death due to arrhythmias.[13,14] Specifically in patients undergoing CRT, Chagas cardiomyopathy has been consistently demonstrated to have worse prognosis in comparison with other etiologies of HF. Martinelli et al. showed that Chagas disease had a 2-fold increased risk of death in 1 year compared with other dilated cardiomyopathies.[15] Passos et al. also demonstrated worse prognosis in combined events in patients with Chagas cardiomyopathy after CRT.[16]

The difference in the percentage of patients with Chagas disease between the groups is due to the fact that intrinsic LBBB is uncommon in this disease. Chagas cardiomyopathy is characterized by a wide variety of conduction abnormalities, notably advanced blocks, and a higher incidence of CRT upgrade is expected in these patients. In fact, in the cohort described by Martinelli et al., there was a 73.9% incidence of induced LBBB in patients with Chagas disease undergoing CRT.[15] In our study, 73% of patients undergoing CRT upgrade had Chagas cardiomyopathy.

To the best of our knowledge, this is the first study to specifically address the impact of CRT upgrade on mortality in a population in which Chagas disease is a prevalent cause of cardiomyopathy. In line with previous publications, Chagas disease was directly associated with an increase in short-term mortality after CRT implantation. However, after multivariate analysis adjusted for possible confounding factors, this worse prognosis was suggested to be due to the higher incidence of CRT upgrade in these patients. Further studies including large cohorts of patients with Chagas cardiomyopathy are needed to confirm this hypothesis. Considering the current scientific evidence, indication for the CRT procedure should be evaluated with great caution in patients with HF secondary to Chagas disease and prior ventricular stimulation.

This study has some limitations. We highlight the single-center design of the study, which may affect its external validity. It was also a non-randomized study that generates hypotheses and is subject to confounding bias.

Conclusion

In this cohort of patients with HF characterized by a high prevalence of Chagas cardiomyopathy, survival outcomes were less favorable among patients who underwent CRT upgrade in comparison with those who received de novo implantation.

Author Contributions

Conception and design of the research: Carvalho W, Passos LCS; Acquisition of data: Carvalho W, Santana GP, BarrosPereira JP, Tapioca FPM; Analysis and interpretation of the data: Carvalho W, Passos LCS, Viana T, Cafezeiro CRF; Statistical analysis: Viana T, Cafezeiro CRF; Writing of the manuscript: Carvalho W, Passos LCS, Viana T, Cafezeiro CRF; Critical revision of the manuscript for content: Passos LCS, Santana GP, Tapioca FPM, Cafezeiro CRF.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

There were no external funding sources for this study.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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