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Cardiac resynchronization therapy outcomes in patients under nonoptimal medical therapy

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Abstract

Background: Cardiac resynchronization therapy (CRT) is indicated in symptomatic heart failure (HF) patients after achieving optimal medical therapy (OMT). However, many patients may not be under OMT when the CRT device is implanted. Here, we evaluate the long-term benefits of CRT in symptomatic HF patients receiving or not OMT.

Methods: We investigated the effect of OMT on HF developing or death in 328 consecutive patients with a CRT device implanted between 2005 and 2015 in a single tertiary center. After the CRT implant, we categorized the patients into three groups: no OMT, OMT at baseline and after 1 year of follow-up, and OMT only at the 1-year follow-up but not at baseline. We used multivariate Cox proportional hazards model to determine the effect of OMT on clinical outcomes.

Results: One hundred and twenty-two patients (37.2%) received OMT prior to CRT. OMT at baseline was not associated with a reduced risk of death or HF (HR 0.72; 95% CI 0.50-1.02; $P = 0.067$) compared with no-basal-OMT patients. After CRT, patients without OMT had a higher risk of death or HF than patients who received OMT in follow-up (HR 1.72, 95% CI 1.07-2.78, $P = 0.025$), and the risk of the patients who received OMT at baseline and at the 1-year follow-up was similar to that of the patients who achieved OMT at the 1-year follow-up (HR 0.90, 95% CI 0.54-1.50, $P = 0.682$).

Conclusion: Basal OMT prior to CRT is not associated with better outcomes in terms of HF/death compared with no basal OMT. The subgroup of patients who achieved OMT at the 1-year follow-up exhibited a reduced risk of HF and death compared with patients who did not.

KEYWORDS

cardiac resynchronization therapy, death, heart failure, optimal medical therapy

1 | INTRODUCTION

Heart failure (HF) is a highly symptomatic syndrome and remains a common cause of poor quality of life, frequent hospitalization and high mortality. Major clinical trials have demonstrated the benefit of cardiac resynchronization therapy (CRT) with a defibrillator (CRT-D) or pacemaker (CRT-P) in terms of clinical outcomes, HF and/or mortality in patients with mild-to-severe symptomatic HF with prolonged QRS width and left ventricular ejection fraction (LVEF) <35% under OMT. CRT has been shown to reduce mortality, morbidity, and improve quality of life in these patients with a life expectancy exceeding 1 year.[1–7]

Optimal medical therapy (OMT) consists of 3 neurohormonal antagonist drugs (angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin II receptor blockers [ARBs], beta-blockers [BB], and mineralocorticoid receptor antagonist [MRAs]) that have been shown to improve survival, reduce hospitalizations for HF, and improve symptoms.[7–14] Nowadays, ACEIs/ARBs, BBs, and MRAs are cornerstones of HF, and they have class I recommendations in clinical guidelines.[7] However, patients may occasionally exhibit side effects or comorbidity conditions with ACEIs/ARBs, BBs, and MRAs; and up-titration of neurohormonal blockers to guideline-recommended doses is not possible.

The addition of CRT should be considered in patients who remain symptomatic despite optimal pharmacological treatment. Our understanding of the benefits of CRT is incomplete, however it has been shown to reduce mortality and HF hospitalizations, symptoms and improve reverse remodeling and quality of life. Up until now, it has been impossible to assess the prognostic impact of CRT in patients without OMT at the time of implant. Here, we evaluate the long-term outcomes of CRT in patients who were not on OMT at the time of implant.

2 | METHODS

This follow-up study included 328 consecutive patients with CRT-D or CRT-P under standard clinical indications in a single tertiary cardiac institution between January 2005 and April 2015. All the patients demonstrated HF symptoms (New York Heart Association (NYHA) functional class II, III, or ambulatory IV symptoms), with ischemic or nonischemic cardiomyopathy, decreased LVEF (≤35%), and prolonged QRS duration (≥120 ms) at the time of implantation. They received pharmacological treatment for HF up-titrated to the maximal tolerated doses according to the European Society of Cardiology guidelines[7] for the management of HF at the discretion of the treating cardiologist.

We registered the baseline characteristics of all of the patients: age, gender, NYHA functional class, atrial fibrillation, underlying heart disease, pharmacological therapy, glomerular filtration rate, and hemoglobin. Electrocardiographic parameters included QRS width and morphology. Echocardiographic parameters included LV end-diastolic (LVEDV) and end-systolic volume (LVESV), LVEF, and left atrial diameter (LAD). The patients were followed up in the Heart Failure Clinic every 3 or 6 months and in the CRT-Device Clinic every 6 months. Electrocardiogram and echocardiogram were also performed at the 6-month and 2-year follow-ups and according to the discretion of the HF cardiologist. Treating cardiologists followed a specified protocol to achieve OMT. Patients with decreases in LVESV exceeding 15% and/or improvements in LVEF of more than 5% were considered to be echocardiographic responders. Patients with improvements in 1 category in NYHA functional class were considered to be clinical responders. Optimal medical therapy was defined as treatment with ACEIs/ARBs, BBs, and MRAs.

The study satisfied all of the requirements of local ethics committees and complied with the Declaration of Helsinki.

2.1 | Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). Categorical data are presented as numbers and percentages. We used the Mann-Whitney and the Kruskal-Wallis tests to compare continuous numerical variables among the groups. The cumulative probability of death and/or HF was calculated using the Kaplan-Meier method. We used the multivariate Cox proportional hazards model to estimate the hazard ratio (HR) and 95% confidence interval (95% CI). We carried out statistical analyses in R using the package "survival," which is freely available at http://cran.r-project.org.

3 | RESULTS

3.1 | Patient characteristics

The study population included 328 patients (253 men and 75 women; mean age: 70.2 ± 9.5 years) who were consecutively implanted with a CRT device at our institution. The mean follow-up duration was 4.2 ± 2.9 years. Of the 328 patients, 122 (37.2%) were on OMT at baseline. The baseline characteristics are listed in Table 1.

Pharmacotherapy at baseline was as follows: 283 patients (86.3%) were on ACEIs/ARBs, 271 patients (82.6%) were on BBs, and 154 patients (47.0%) were on MRAs. Combinations of drugs prior to CRT were as follows: 112 patients (34.1%) were on ACEIs/ARBs, BBs, and MRAs; 119 patients (36.3%) were on ACEIs/ARBs and BBs; 9 patients (2.7%) were on BBs and MRAs; 20 patients (6.1%) were on ACEIs/ARBs and MRAs; 46 patients (14.0%) were on ACEIs/ARBs or BBs or MRAs; and 12 patients (3.7%) were not taking any drugs. Changes in echocardiographic, electrical, and clinical variables during follow-up are listed in Table 1.

> We investigated the causes why 206 patients were not under OMT at the time of CRT implant. The most frequent cause was chronic kidney disease with or

TABLE 1 Differences in baseline characteristics and clinical, electrical, and echocardiographic variables of patients on baseline and nonbaseline optimal medical therapy

	OMT (n = 122)	Non-basal OMT (n = 206)	*P*-value
Gender, male, n (%)	96 (78.7)	157 (76.2)	0.606
Age, y	68.7 ± 9.5	71.1 ± 9.4	0.030
Ischemic cardiomyopathy, n (%)	47 (38.5)	72 (35.0)	0.515
CRT-D, n (%)	66 (54.1)	106 (51.5)	0.643
NYHA class, n (%)			
II	39 (32.0)	40 (19.4)	0.030
III	78 (63.9)	152 (73.8)	
IV	5 (4.1)	14 (6.8)	
Diabetes, n (%)	30 (24.6)	47 (22.8)	0.714
Atrial fibrillation, n (%)	43 (35.2)	80 (38.8)	0.516
AV node ablation, n (%)	8 (6.6)	17 (8.3)	0.576
Glomerular filtration rate, mL/(min × 1.73 m^2)	64.2 ± 22.8	58.6 ± 24.5	0.458
Hemoglobine level, g/dL	13.3 ± 1.2	13.10 ± 1.8	0.241
Coronary sinus vein, n (%)			
Anterior	19 (15.7)	50 (24.8)	0.021
Lateral	61 (50.4)	109 (54.0)	
Posterior	41 (33.9)	43 (21.2)	
QRS width, ms	164.7 ± 27.1	161.2 ± 25.6	0.235
LVEDV basal, mL	238.8 ± 76.3	161.0 ± 64.8	0.008
LVESV basal, mL	176.7 ± 62.6	158.6 ± 58.2	0.013
LVEF basal, %	26.4 ± 7.2	27.6 ± 7.9	0.188
QRS width post, ms	153 ± 26	156 ± 29	0.440
LVEF post,%	38.3 ± 12.7	38.9 ± 12.9	0.614
LVEDV post, mL	182.3 ± 80.1	169.8 ± 66.6	0.188
LVESV post, mL	118.1 ± 73.1	106.1 ± 54.1	0.002
LA post, mm	49.7 ± 9.7	48.5 ± 9.7	0.367
ΔLVEF, %	11.5 ± 12.7	12.1 ± 12.9	0.704
ΔLVEF >5%, n (%)	84 (69.4)	130 (63.1)	0.246
ΔLVESV, mL	51.6 ± 65.8	46.5 ± 58.1	0.548
ΔLVESV >15%, n (%)	72 (80.9)	108 (83.7)	0.589
ΔQRS, ms	11 ± 31	5 ± 36	0.083
Clinical response, n (%)	96 (78.7)	144 (69.9)	0.083
Clinical response, n (%)			
Worse	3 (1.5)	1 (0.8)	0.229
No change	59 (28.6)	25 (20.5)	
Improvement 1 class	122 (59.2)	76 (62.3)	
Improvement 2 class	22 (10.7)	20 (16.4)	

AV, atrio-ventricular; CRT-D, Defibrillator with Cardiac Resynchronization Therapy; LA, left atrium; LBBB, left bundle branch block; LVEF, left ventricular eyection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; NYHA, New York Heart Association; OMT, optimal medical therapy; Δ, changes.

without hyperpotasemia in 76 patients (36.6%). The second cause was bradycardia (sinus node dysfunction (39 patients) or high degree atrioventricular block (18 patients) with 57 patients (27.7%)). The third cause was symptomatic hypotension (46 patients (22.3%)). Other reasons were: the occurrence of ventricular arrhythmias in patients with depressed LVEF in whom an implantable cardioverter defibrillator was indicated (24 patients (11.6%)) and bronchial hyperactivity (3 patients (1.5%)).

3.2 | Basal OMT and HF/death

Heart failure or death occurred in 56 out of 122 patients (45.9%) receiving OMT at baseline and in 123 out of 206 patients (59.7%) not receiving OMT at baseline. Patients on OMT showed a significant trend to lower risk of the composite endpoint ($P = 0.098$). Similar results were obtained when we analyzed HF hospitalizations and death separately (Figure 1).

Multivariable Cox proportional hazards model analyses revealed that basal OMT patients had a similar risk of HF/death during long-term follow up (HR 0.73, 95% CI 0.50-1.02, $P = 0.067$) as no-basal-OMT patients. There was also a similar risk for HF (HR 1.40, 95% CI 0.91-2.16, $P = 0.126$) and death (HR 0.72, 95% CI 0.48-2.16, $P = 0.180$) in both groups of basal treatment.

3.3 | Up-titration of neurohormonal blockers. OMT in follow-up

Up-titration in neurohormonal blockers 1 year after CRT implantation was evaluated. 35 patients died in the first year, and they were excluded. At follow-up, 82 patients (28%) achieved OMT only after CRT, 105 patients (35.8%) had no OMT and 106 patients (36.2%) maintained baseline OMT after CRT. Patients on OMT at the 1-year follow-up were younger, had higher baseline hemoglobin and glomerular filtration rates, and had larger left ventricles. Furthermore, they were in a worse functional class than patients who had received basal OMT, similar to the functional class of the non-OMT group. A poorer glomerular filtration rate was observed in non-OMT patients compared with basal OMT patients and patients with OMT at follow-up. The position of the LV electrode in the coronary sinus was significantly different between the basal and nonbasal OMT groups; the anterior location was more frequent in the no-basal-OMT group, and the posterior location was more frequent in the basal OMT group. However, these differences are not observed after the optimization of pharmacological treatment. Table 2 lists the baseline characteristics and changes according to the treatment in the first year of follow-up.

In the Cox hazards proportion model for death or HF, and death and HF separately, OMT after 1 year of follow-up was an independent predictor of events (Table 3 and Figure 2). In fact, patients without OMT had a higher risk of death or HF than patients with OMT at the 1-year follow-up (HR 1.72, 95% CI 1.07-2.78, $P = 0.025$), and the risks of patients with basal OMT and OMT at the 1-year follow-up were similar (HR 0.90, 95% CI 0.54-1.50,

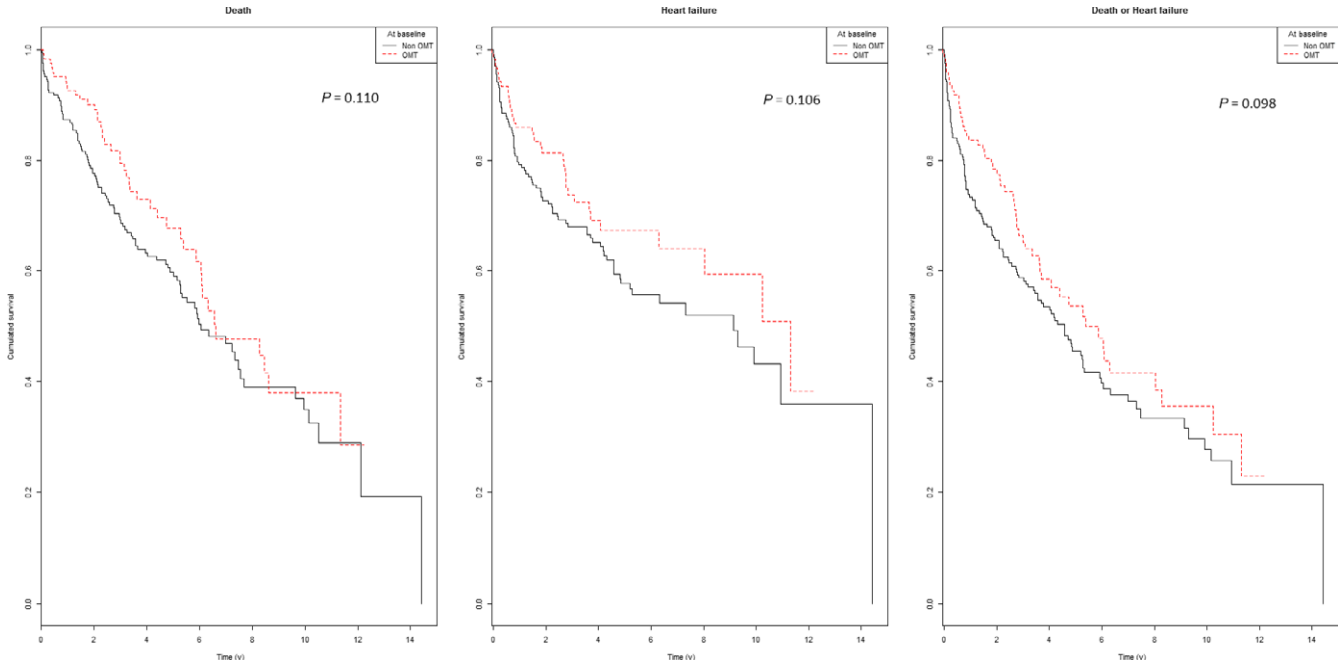

FIGURE 1 Cumulative survival free of death, heart failure or heart failure and optimal medical therapy at baseline

P = 0.682). However, the risk of HF hospitalizations in long follow-up was similar for all of the groups (Table 3, Figure 2).

4 | DISCUSSION

The primary finding of this follow-up study is that patients with no OMT at baseline who had CRT implanted experienced the same clinical outcomes of HF/death compared with patients on OMT at baseline. Furthermore, those patients who achieved OMT at the 1-year follow-up after implantation had a lower risk of HF/death than patients who remained on no-OMT. This study suggests, for the first time, that CRT may promote medical treatment optimization early after implantation and that this optimization is associated with a better outcome.

Combined treatment with OMT and biventricular pacing has been shown to invoke marked reduction in HF/death events, which appear very early and are sustained.[7–16] This benefit has been observed in patients with mild-to-severe HF symptoms in randomized studies.[1–6] The European Society of Cardiology Guidelines for clinical practice of HF[7] recommend ACEIs and BBs as an initial step in symptomatic HF, and both of these treatments have been shown to reduce mortality and HF hospitalizations (Class of Recommendation I, Level of Evidence A). In addition, MRAs are recommended when patients remain symptomatic under ACEIs and BBs (Class of Recommendation I, Level of Evidence A). Cardiac resynchronization therapy has been recommended in patients with reduced LVEF and prolonged QRS who remain symptomatic despite optimal pharmacological therapy. However, some patients remain symptomatic and may not be treated with all of the recommended pharmacological treatments for comorbidity conditions or side effects such as hypotension, which inhibits up-titrating to the maximum tolerated evidence-based doses.[7–14] In the REVERSE study, only 35% of patients were on the target dose of BBs, and 60% were receiving 50% of the target dose.[6] Achieving the target doses of neurohormonal treatment has clinical relevance; Schmidt et al[17] showed that the use of higher dosages of neurohormonal blockers was associated with reduction of morbidity and mortality after CRT implantation. These authors also demonstrated that super-responders were treated with higher doses of ACEIs/ARBs or BBs. Our results suggest that achieving OMT early after CRT implantation had a prognostic value for reducing death and/or HF hospitalizations; and efforts to achieve OMT necessary. Cardiac resynchronization therapy implantation may help optimize pharmacological treatment during the follow-up period. Such a situation should be recommended as a target in patients with no OMT at the time of implant.

The basal pharmacological treatment in large-scale clinical trials—COMPANION,[2] CARE-HF,[3] MADIT-CRT[4] and RAFT[5]—was as follows: 95%, 90%, 77%, and 96%, respectively, with ACEIs/ARBs; 73%, 68%, 93%, and 90%, respectively, with BBs; 54%, 55%, 32% and 42%, respectively, with MRAs. In our series, the percentage of patients on pharmacological treatment prior to CRT was similar (ACEIs or ARBs: 86%, BBs: 83%, MRAs: 47%) to the percentages observed in the large clinical trials. Triple-pharmacological treatment was achieved in 122 patients (37%) at baseline and improved up to 198 patients (60%) 1 year after CRT implantation.

Thus far, scientific attention has largely focused on refining preimplantation patient selection to predict a favorable response to CRT because 30% of patients do not benefit from CRT. Optimization of preimplant HF pharmacological treatment has been considered to be a measure of response of CRT.[18] However, we have shown that the optimization of pharmacological treatment during the first year of follow-up was associated with a relative risk reduction of HF/

TABLE 2 Differences in baseline characteristics and clinical, electrical, and echocardiographic variables between patients on basal and 1-year of follow-up optimal medical therapy, optimal medical therapy only at 1-year of follow-up and no-optimal medical therapy

	no-OMT 35.8% (n = 105)	Basal and 1-year follow-up OMT 36.2% (n = 106)	OMT at 1-year follow-up 28.0% (n = 82)	*P*-value
Gender: male, n (%)	84 (80.0)	83 (78.3)	59 (72.0)	0.403
Age, y	73.1 ± 7.7	67.9 ± 9.8	68.9 ± 9.9	0.000
Ischemic cardiomyopathy, n (%)	43 (41.0)	41 (38.7)	22 (26.8)	0.109
CRT-ICD, n (%)	61 (58.1%)	57 (53.8)	39 (47.6)	0.358
NYHA class, n (%)				
II	17 (16.2)	39 (36.8)	21 (25.6)	0.006
III	81 (77.1)	62 (58.5)	60 (73.2)	
IV	7 (6.7)	5 (4.7)	1 (1.2)	
Diabetes, n (%)	28 (26.7)	24 (22.6)	16 (19.5)	0.509
Atrial fibrillation, n (%)	40 (38.1)	35 (33.0)	31 (37.8)	0.698
AV node ablation, n (%)	8 (7.6)	7 (6.6)	7 (8.5)	0.882
Glomerular filtration rate, mL/(min × 1.73 m^2)	54.0 ± 21.2	66.1 ± 23.1	68.7 ± 24.3	0.000
Hemoglobine level, g/dL	12.8 ± 1.7	13.4 ± 1.6	13.7 ± 1.5	0.000
Coronary sinus vein, n (%)				
Anterior	28 (27.2)	17 (16.2)	16 (19.8)	0.131
Lateral	49 (47.6)	53 (50.5)	48 (59.3)	
Posterior	26 (25.2)	35 (33.3)	17 (16.6)	
QRS width prior, ms	162.7 ± 26.8	164.5 ± 26.4	162.2 ± 26.4	0.729
LBBB, n (%)	62 (59.0)	60 (56.6)	57 (69.5)	0.171
LVEDV basal, mL	214.8 ± 63.4	241.1 ± 76.7	224.0 ± 72.2	0.051
LVESV basal, mL	157.2 ± 54.1	179.6 ± 63.4	165.9 ± 63.7	0.042
LVEF basal, %	27.8 ± 7.9	26.3 ± 7.2	27.1 ± 7.8	0.097
QRS width post, ms	156.9 ± 27.6	154.3 ± 26.9	152.4 ± 32.4	0.594
LVEF post, %	39.2 ± 13.3	36.9 ± 11.8	37.7 ± 11.8	0.106
LVEDV post, mL	174.1 ± 73.3	193.0 ± 75.6	193.0 ± 70.3	0.180
LVESV post, mL	106.8 ± 59.1	113.7 ± 69.6	108.3 ± 57.2	0.796
ΔLVEF, %	11.0 ± 13.9	13.2 ± 13.4	13.4 ± 12.8	0.534
ΔLVEF >5%, n (%)	67 (63.8)	75 (70.8)	54 (65.9)	0.548
ΔLVESV, mL	44.5 ± 55.7	58.3 ± 66.9	52.6 ± 63.2	0.392
ΔLVESV >15%, n (%)	50 (82.0)	65 (83.3)	54 (85.7)	0.849
ΔQRS, ms	6 ± 34	10 ± 29	8 ± 35	0.558
Clinical response, n (%)	76 (72.4)	85 (80.2)	61 (74.4)	0.393
Clinical response, n (%)				
Worse	1 (1.0%)	0 (0.0)	1 (1.2)	0.562
No change	28 (26.7)	21 (19.8)	20 (24.4)	
Improvement 1 class	61 (58.1)	68 (64.2)	54 (65.9)	
Improvement 2 class	15 (14.3)	17 (16.0)	7 (8.5)	

AV, atrio-ventricular; CRT-D, Defibrillator with Cardiac Resynchronization Therapy; LA, left atrium; LBBB, left bundle branch block; LVEF, left ventricular eyection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left Ventricular end systolic volume; NYHA, New York Heart Association; OMT, Optimal medical therapy; Δ, changes.

death, which suggests a complementary effect of CRT and up-titration of pharmacological therapy. The reason for this improvement might be that CRT provides acute hemodynamic improvement,[19–22] with an increase in cardiac output and a reduction in pulmonary capillary wedge and improvement in the mechanical activation sequence. Cardiac resynchronization therapy also supports systemic blood pressure and heart rate, enabling an increase in the doses of drugs without the associated risk of lethal bradycardia and

TABLE 3 Multivariate Cox proportional hazards model for death, HF hospitalization and death/HF hospitalization in patients regarding to optimal medical therapy at baseline and at 1 y of follow-up

Variable	HR	95%	*P*-value
Death			
Age	1.07	1.04-1.10	0.000
Male	1.78	0.98-3.21	0.058
Ischemic cardiomyopathy	1.32	0.84-2.10	0.231
NYHA class			0.719
II	1		
III	1.21	0.63-2.33	
IV	1.57	0.51-4.82	
Coronary sinus vein			0.067
Anterior	1		
Lateral	0.73	0.45-1.04	0.195
Posterior	0.44	0.22-0.89	0.022
LVEDV	1.02	1.05-1.08	0.001
LVESV	1.00	0.99-1.01	0.666
Glomerular filtration rate	0.99	0.98-1.01	0.886
Hemoglobine	0.94	0.82-1.08	0.387
OMT			0.000
Basal and 1-year of FU OMT	1		
No OMT	2.95	1.55-5.59	0.001
OMT only at 1-year FU	1.14	0.57-2.27	0.719
HF hospitalization			
Age	1.02	0.98-1.05	0.230
Male	2.64	1.42-4.90	0.002
Ischemic cardiomyopathy	1.08	0.68-1.73	0.749
NYHA class			0.615
II	1		
III	1.30	0.72-2.33	0.381
IV	1.55	0.53-4.54	0.426
Coronary sinus vein			0.715
Anterior	1		
Lateral	0.87	0.50-1.53	0.632
Posterior	0.75	0.39-1.48	0.413
LVEDV	1.01	0.99-1.02	0.227
LVESV			
Glomerular filtration rate	0.98	0.97-0.99	0.008
Hemoglobine	1.01	0.87-1.17	0.910
OMT			0.125
Basal and 1-year FU OMT	1		
No OMT	1.10	0.64-1.89	0.726
OMT only at 1-year FU	0.63	0.36-1.13	0.125
HF hospitalizations/Death			
Age	1.04	1.02-1.06	0.000
Male	1.79	1.10-2.94	0.022
Ischemic cardiomyopathy	1.18	0.80-1.75	0.399
NYHA class		0.38-2.83	0.983
II	1		
III	1.05		0.851
IV	1.05		0.931
Coronary sinus vein			0.212
Anterior	1		
Lateral	0.84	0.55-1.30	0.440
Posterior	0.61	0.35-1.06	0.079
LVEDV	1.01	1.00-1.02	0.011
LVESV	0.99	0.98-1.01	0.882
Glomerular filtration rate	0.9	0.98-1.01	0.263
Hemoglobine	1.01	0.88-1.13	0.989
OMT			**0.007**
Basal and 1-year FU OMT	1		
No OMT	1.72	1.07-2.78	**0.025**
OMT only at 1-year FU	0.90	0.54-1.50	**0.682**

P value < 0.05 was considered to be statistically significant (bold).
95% CI, 95% confidence interval; HR, hazard ratio; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; OMT, optimal medical treatment.
Gender: 0: female, 1: male. Etiology: 0: nonischemic, 1: ischemic. Functional class: NYHA II as a reference. Coronary sinus vein: anterior vein as a reference; OMT: OMT at follow-up as a reference.

hypotension. So, in CARE-HF,[3] 25% of patients had a resting rate of ≤60 beats per minute at baseline; CRT could prevent symptoms of bradycardia in addition to the benefit of resynchronization. Up-titration of neurohormonal treatment after CRT has been described in other studies with consistent findings. A small study reported a major reduction in hospitalizations and mortality with increasing dosages of ACEIs/ARBs after CRT.[23] Mullens et al[24] demonstrated, in a nonrandomized, single-center study with 114 patients, that optimization of device programming, arrhythmia management, lead reposition, or up-titration of medical therapy after CRT improved long-term outcomes and reverse remodeling.

Cardiac resynchronization therapy has demonstrated benefit in HF patients who are very highly symptomatic (NYHA class III or IV[2,3]), less symptomatic (NYHA class II or III[5]), mildly symptomatic or even asymptomatic (NYHA class I or II[4–6]) in terms of reducing hospitalizations and mortality and improving functional class. However, on the other hand, CRT promotes LV reverse remodeling and a decrease in LVESV exceeding 15% has been shown to have a clinical impact on mortality and morbidity reduction in asymptomatic or symptomatic patients.[25–27] According to our results, mildly or asymptomatic patients might benefit from CRT in clinical outcomes by exhibiting a reduction in HF hospitalizations or mortality when the standard therapy for HF (ACEI/ARB and/or BB) does not improve LVEF beyond 35%-40%, independent of HF symptoms. Regrettably, only 265 patients (14.5%) in the MADIT CRT[4] trial and 110 patients (18%) in the REVERSE[6] trial were in NYHA class I. Therefore, this low percentage of patients in NYHA class I, does not allow us to

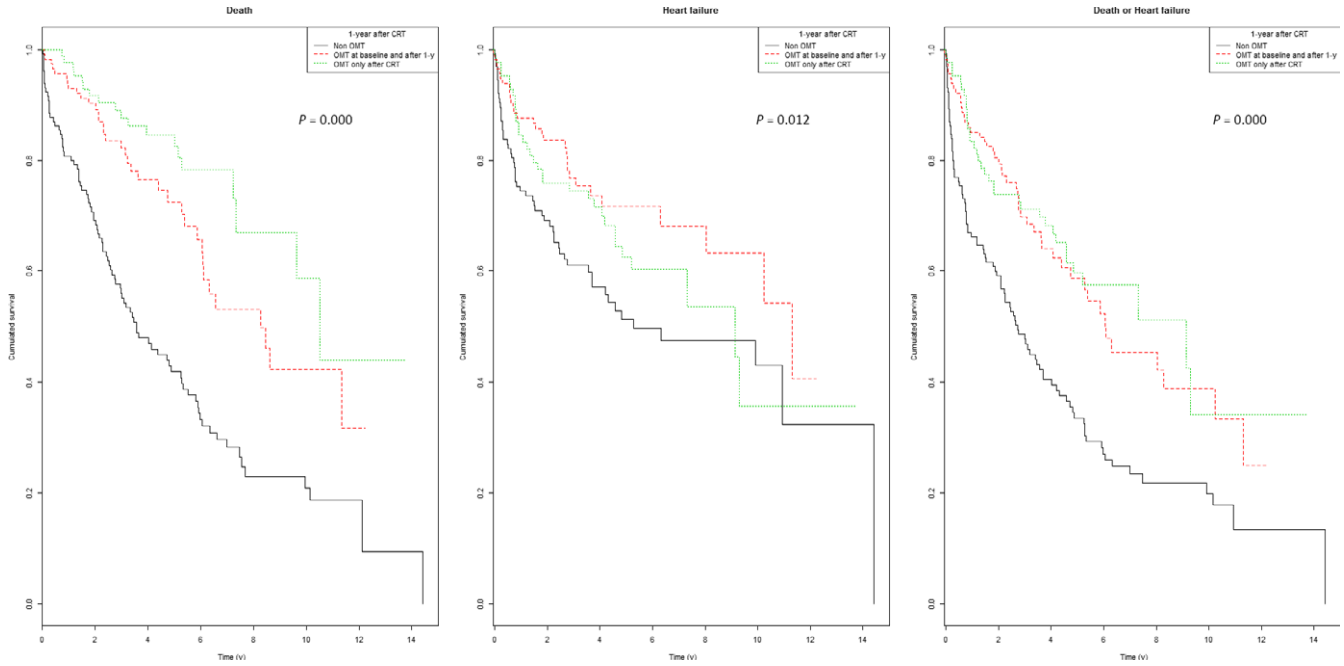

FIGURE 2 Cumulative survival free of death, heart failure and death or heart failure and optimal medical therapy at the 1-year of follow-up after the cardiac resynchronization therapy (CRT) implantation

extend further indication of CRT to asymptomatic patients. In addition, a MADIT-CRT substudy assessed the association among pharmacological therapy, outcome, and reverse remodeling. Only ACEI/ARB use was associated with a decreased risk of HF or death, and ACEI/ARB use was directly correlated with LVEF and LVESV. However, this correlation was not demonstrated with BBs, and diuretic use was associated with an increased risk of HF hospitalization or death and an inverse correlation with changes in LVEF and LVESV. Ventricular remodeling and hemodynamic improvement of CRT might explain the reduction of HF/mortality in these patients,[28] regardless of pharmacological therapy. In our study, the optimization of pharmacological treatment with CRT was associated with clinical improvement over the long-term and cardiovascular events compared with no OMT. However, no differences in echocardiographic response have been observed at the 1-year follow-up. The echocardiographic response might be delayed after optimization of pharmacological and mechanical therapies or might require a longer period of therapy before improvements are detectable.[29]

The selection of the optimal candidates for CRT is critical, but the presence of baseline OMT might not be an exclusion criterion. It is clinically important to recognize patients who might tolerate up-titration of neurohormonal blockers after CRT implantation because this subgroup of patients exhibits better outcomes.

5 | LIMITATIONS

This investigation was a retrospective study conducted at a single center. As a consequence, the patient sample size was limited. Adjustment of pharmacological treatment was at the discretion of the HF team. However, these aspects are inherent to any real-world analyses. Therefore, our results need to be confirmed in future large, multicenter trials.

6 | CONCLUSION

In this follow-up study, basal OMT prior to CRT implant was not associated with a better outcome. Optimal medical therapy achieved at the 1-year follow-up was associated with a reduced risk of HF/death compared with no-OMT patients. Our results suggest that efforts should be made to achieve medical treatment optimization after CRT implantation to improve outcomes.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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