

Effect of Sacubitril/Valsartan on All-Cause Mortality Reduction in Patients Undergoing Cardiac Resynchronization Therapy: SALVA-CRT

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Abstract

Background: Cardiac resynchronization therapy (CRT) is indicated for patients with heart failure with reduced ejection fraction (HFrEF) receiving conventional triple therapy (CTT). Although sacubitril/valsartan (S/V) is a cornerstone of modern triple therapy (MTT) for HFrEF, its effectiveness in patients undergoing CRT implantation has not been adequately evaluated.

Objective: To compare all-cause mortality between CRT recipients on CTT and those on MTT, with a minimum follow-up of 1 year.

Methods: Prospective, observational cohort including patients undergoing a first CRT implantation. Inclusion criteria were left ventricular ejection fraction (LVEF) $\leq 35\%$ and bundle branch block with QRS ≥ 150 ms, with prior use of either CTT or MTT. Patients who discontinued any medication, initiated a sodium-glucose cotransporter-2 inhibitor (SGLT2i), or crossed over between CTT and MTT during follow-up were excluded. Statistical analyses used the unpaired Student's *t* test ($p < 0.05$ for significance). Cox regression was applied to variables potentially associated with the outcome ($p < 0.1$).

Results: From 2017 to 2022, 425 CRT implantations were performed; 58 (13.6%) patients were excluded. Of the 367 analyzed, 286 (78%) were on CTT and 81 (22%) on MTT. Mean age was 61 (± 12) years; mean LVEF was 26% (± 6); Chagas disease was the most prevalent etiology (34.3%). Mean follow-up was 58 (± 8) months, with 62 deaths (16.9%): 59 (21%) in the CTT group and 3 (3.7%) in the MTT group. The HR was 1.27 (95% CI 1.17–1.39) for CTT and 0.18 (95% CI 0.06–0.58) for MTT. In multivariable analysis, CTT use was the only independent predictor of mortality (HR 5.83; 95% CI 1.81–18.70; $p = 0.003$).

Conclusion: MTT including S/V significantly reduced all-cause mortality in patients undergoing CRT implantation.

Keywords: Mortality; Systolic Heart Failure; Cardiac Resynchronization Therapy.

Introduction

Optimized medical therapy should be established prior to the implantation of cardiac resynchronization therapy (CRT).¹ Ideally, patients should be receiving the maximum tolerated doses of medications proven to improve prognosis in heart failure (HF) with reduced ejection fraction (HFrEF) at the time of CRT implantation.² Among these treatments, conventional triple therapy (CTT) — comprising angiotensin-converting enzyme inhibitors (ACEi), beta-blockers, and spironolactone — stands out. In contrast, modern triple therapy (MTT) incorporates

the angiotensin receptor-neprilysin inhibitor (ARNi) sacubitril/valsartan (S/V) as a replacement for ACEi.^{3,4}

Although these pharmacologic strategies serve as adjuvants to CRT, both clinical trials and real-world studies have demonstrated the superiority of MTT over CTT.^{4,5} Nevertheless, some clinical guidelines still recommend ACEi as first-line therapy for HF.

Almost half of patients undergoing CRT are thought to not achieve the expected clinical benefit. Real-world data suggest that therapeutic inertia and the underutilization of modern medications may be associated with both high nonresponse rates and increased risk of adverse outcomes following CRT.^{6,7}

Despite numerous studies supporting the efficacy of S/V in HFrEF treatment, few patients in CRT trials were actually receiving this medication. As a result, there is still no strong evidence supporting the mandatory use of S/V prior to CRT indication.⁸⁻¹³

Therefore, the aim of this study was to compare all-cause mortality over a minimum follow-up period of 1 year between patients undergoing CRT who were treated with CTT and those treated with MTT.

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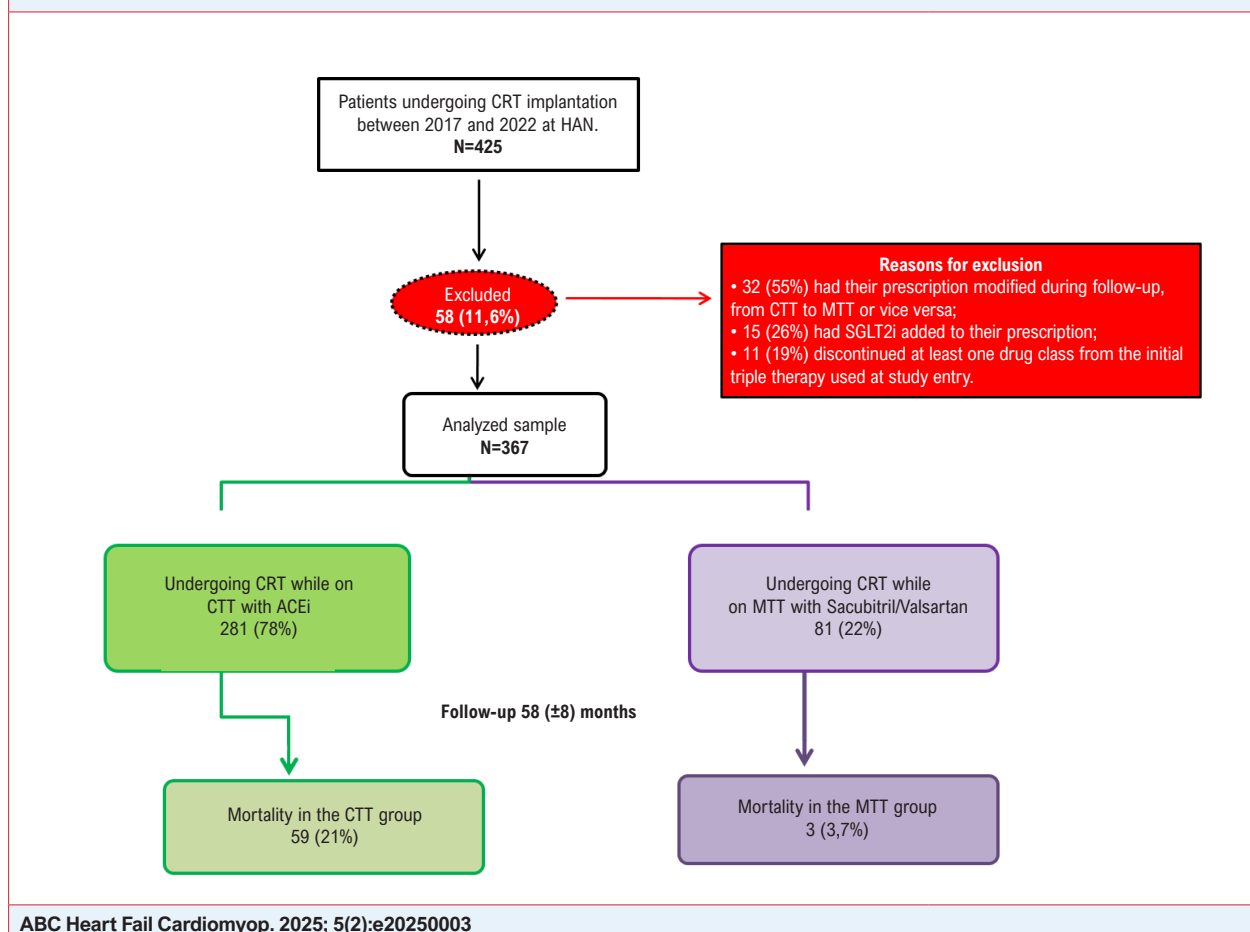
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Central Illustration: Effect of Sacubitril/Valsartan on All-Cause Mortality Reduction in Patients Undergoing Cardiac Resynchronization Therapy: SALVA-CRT

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Study flowchart. CRT: cardiac resynchronization therapy; CTT: conventional triple therapy (use of angiotensin-converting enzyme inhibitors [ACEi] combined with beta-blockers and spironolactone); S/V: Sacubitril/Valsartan; MTT: Modern triple therapy (use of S/V combined with beta-blockers and spironolactone); NYHA: New York Heart Association; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support.

Objective

To compare all-cause mortality over a minimum follow-up period of 1 year between patients undergoing CRT implantation who were receiving CTT and those receiving MTT.

Method

This was a prospective, observational, single-center cohort study including patients with HFrEF consecutively referred for CRT implantation between 2017 and 2022 at Hospital Ana Nery, Universidade Federal da Bahia, a reference center for cardiovascular diseases and the only institution in the state of Bahia accredited by the Brazilian Unified Health System (Sistema Único de Saúde, SUS) to implant high-cost cardiac implantable electronic devices.

Definition of variables and group characteristics

CTT was defined as the use of an ACEi combined with a beta-blocker and spironolactone, whereas MTT was defined as the use of S/V combined with a beta-blocker and spironolactone.

Patients were grouped according to the triple therapy they were receiving prior to CRT implantation, which was maintained throughout the follow-up period. Thus, two groups were formed: one composed of patients on continuous CTT and the other on continuous MTT.

Inclusion criteria

Patients were eligible if they were older than 18 years, had left ventricular ejection fraction (LVEF) $\leq 35\%$, interventricular dyssynchrony with QRS ≥ 150 ms, New York Heart Association (NYHA) functional class II or III, and were on either CTT or MTT at the time of CRT implantation.

Exclusion criteria

Patients were excluded if, for any reason during follow-up, they discontinued any of the medications included in the CTT or MTT initiated at baseline, began using an sodium-glucose transport protein 2 (SGLT2i), or switched between groups (from CTT to MTT or vice versa).

Admission flow, logistics, and follow-up procedures

Patients were admitted from other hospitals or referred by outpatient clinics. After evaluation and indication for CRT implantation, candidates were assigned according to the pharmacological therapy in use (CTT or MTT). Follow-up was conducted by a multidisciplinary team (nurse, social worker, pharmacist, and psychologist) through monthly telephone or messaging app contact and in-person visits every 6 months or during regular appointments with the attending physician.

Data collection and variables of interest

The clinical variables assessed included prior medications, NYHA functional class, comorbidities, HF etiology, and anthropometric data. Imaging tests consisted of a transthoracic echocardiogram performed within 1 year prior to admission, prioritizing LVEF obtained by Simpson's method (apical 4- and 2-chamber views). Electrocardiographic reports supporting CRT indication were also considered, with conduction abnormalities classified as native LBBB, pacemaker- or ICD-induced LBBB, or absence of LBBB. Regardless of the block type, QRS duration had to be ≥ 150 ms.

Laboratory variables of interest included serum creatinine and estimated glomerular filtration rate (eGFR) based on the CKD-EPI equation, obtained within 24 hours prior to implantation.

Outcome

All-cause mortality with a minimum follow-up of 1 year.

Statistical analysis

Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Variables with normal distribution were expressed as mean $\pm$ standard deviation and compared using the unpaired Student's *t*-test. Non-normally distributed variables were presented as median and interquartile range and compared using the Mann-Whitney test. Categorical variables were presented as absolute and relative frequencies and compared using the chi-square test. Kaplan-Meier survival curves were used to estimate survival, with comparisons between groups conducted using the log-rank test. For multivariate analysis, a Cox regression model was applied, including variables with a potential association with the outcome ($p < 0.1$). Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

The study was approved by the Institutional Research Ethics Committee, in accordance with Resolution No. 466/2012 of the Brazilian National Health Council. All procedures followed the principles of the Declaration of Helsinki.

Results

Between 2017 and 2022, a total of 425 patients were admitted, of whom 58 (11.6%) were excluded (Central Illustration). Exclusions occurred throughout the follow-up period, which had a mean duration of 58 (± 8) months. Among the excluded patients, 32 (55%) were removed due to a change in prescription from CTT to MTT, 15 (26%) due to the introduction of an SGLT2i, and 11 (19%) due to the discontinuation of at least 1 class of medications within the prescribed triple therapy regimen.

Among the 367 patients included in the final analysis, 286 (78%) were on CTT and 81 (22%) on MTT. The Table 1 shows the baseline clinical characteristics, which include a predominance of males (57%), a mean age of 61 years (± 12), Chagas disease as the most prevalent etiology (34.3%), and a mean LVEF of 26% (± 4).

Overall mortality was 62 patients (16.9%), with 59 (21%) deaths in the CTT group and only 3 (3.7%) in the MTT group (Figure 1), representing a statistically significant difference (log-rank test, $p = 0.001$).

In multivariate analysis, CTT use was identified as an independent predictor of mortality (HR 5.83; 95% CI 1.81-18.70; $p = 0.003$), whereas MTT use was significantly associated with protection against the outcome (HR 0.71; 95% CI 0.44-0.67; $p = 0.002$) (Table 2).

Discussion

Our cohort revealed relevant findings. After multivariate analysis, patients undergoing CRT implantation while on MTT with S/V showed significant protection against the primary outcome, whereas those on CTT had an increased risk of mortality.

Eligibility for new therapies in patients with implanted devices remains underexplored in the literature but appears promising, despite the scarcity of dedicated studies. Medication optimization is feasible for several reasons: the proven efficacy and safety of these drugs, strong support in clinical guidelines, and, in the Brazilian context, their availability free of charge through government programs. The PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, which compared S/V to enalapril, was discontinued early due to the superiority of S/V, with a significant reduction in all-cause mortality.¹⁴ Despite the high level of evidence and strong international guideline recommendations, MTT remains underutilized. In our sample, the proportion of patients who maintained MTT use was 114 (26%), similar to that reported in literature, which ranges from 23% to 44%.^{2-4,13}

To date, no prospective study has evaluated mortality in patients undergoing CRT using CTT versus MTT. A systematic review of 38 studies assessed therapy optimization and clinical outcomes after CRT implantation ($n = 27$ studies), with sample sizes ranging from 50 to 7,932 patients and mean follow-up periods from 6 to 70 months. Among them, only 1 French retrospective study ($n = 243$) reported the frequency of CTT use, whereas S/V use was documented in 23% to 44% of CRT patients.¹³

Table 1 – Clinical and demographic characteristics of patients undergoing CRT, according to type of therapy used

Variable	CTT (n = 286)	MTT (n = 81)	p-value
Male sex, n (%)	165 (57.7%)	44 (54.3%)	0.590
Age, mean (±SD)	61 (±12)	61 (±12)	0.963
NYHA class II, n (%)	106 (37.0%)	29 (35.8%)	0.836
NYHA class III, n (%)	180 (63.0%)	52 (64.2%)	0.872
CRT-D implantation, n (%)	186 (65.0%)	53 (65.4%)	0.948
Native LBBB, n (%)	163 (57.0%)	50 (61.7%)	0.445
Device-induced LBBB (upgrade), n (%)	63 (22.0%)	18 (22.2%)	0.330
No LBBB, n (%)	60 (21.0%)	13 (16.1%)	0.813
Hypertension, n (%)	213 (74.5%)	56 (69.1%)	0.339
Diabetes mellitus, n (%)	91 (31.8%)	27 (33.3%)	0.797
Atrial fibrillation, n (%)	61 (21.3%)	11 (13.6%)	0.090
Prior myocardial infarction, n (%)	57 (20.0%)	12 (14.8%)	0.270
Prior stroke, n (%)	47 (16.4%)	13 (16.1%)	0.934
Chronic obstructive pulmonary disease, n (%)	18 (6.3%)	8 (9.9%)	0.268
Chagas disease etiology, n (%)	105 (36.7%)	21 (26.0%)	0.059
Ischemic etiology, n (%)	46 (16.0%)	11 (13.6%)	0.571
Myocarditis, n (%)	41 (14.3%)	12 (14.8%)	0.615
Other known etiologies, n (%)	94 (32.9%)	44 (54.3%)	0.036
Use of digoxin, n (%)	57 (20.0%)	15 (18.5%)	0.776
Use of furosemide, n (%)	230 (80.4%)	61 (75.3%)	0.343
Body mass index, mean (±SD)	24 (±4)	24 (±5)	0.448
LVEF, mean (±SD)	26% (±6)	25% (±6)	0.703
Glomerular filtration rate, mean (±SD)	69 (±25)	67 (±25)	0.997
MAGGIC score, mean (±SD)	15.5 (±8.6)	16.2 (±8.6)	0.444

AF: atrial fibrillation; CRT: cardiac resynchronization therapy; CTT: conventional triple therapy; MTT: modern triple therapy; LBBB: left bundle branch block; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure.

We also observed a trend toward a higher incidence of atrial fibrillation (AF) in the CTT group compared to the MTT group (21.3% vs. 13.5%; $p = 0.09$). Although this difference did not reach statistical significance and AF was not an independent predictor of mortality in the multivariate analysis, this finding warrants attention given its clinical relevance. AF has been associated in several studies with poorer response to CRT, which may partially contribute to the outcomes observed in this study.^{13,14} Newly diagnosed or persistent AF has been linked to reduced LV reverse remodeling and less improvement in ejection fraction following CRT. Moreover, AF increases the risk of adverse events, such as inappropriate ICD shocks and HF-related hospitalizations.¹⁵

Similarly, Chagas etiology showed a numerically higher frequency in the CTT group compared to the MTT group (36.7% vs. 26.0%; $p = 0.059$), with a trend toward statistical significance. Although it was not identified as an independent

predictor of mortality in the multivariate analysis, this finding is clinically relevant, considering the impact of Chagas disease in patients with HF. Chagas cardiomyopathy (CCM) often presents with distinctive electrocardiographic and structural features that may negatively affect the response to CRT. In a cohort study, patients with CCM had twice the risk of death compared to those with dilated cardiomyopathy. Furthermore, these patients showed a lower response to CRT, both in terms of functional capacity improvement and ventricular remodeling.¹⁶ Ventricular arrhythmias, commonly observed in CCM, pose an additional challenge and are associated with high rates of appropriate implantable cardioverter-defibrillator therapies and electrical storm episodes.¹⁷

Despite the lower mortality observed in the group using MTT with S/V, it is important to note that a substantial proportion of patients did not reach the target dose of the drug. Among the 75 patients undergoing CRT while on

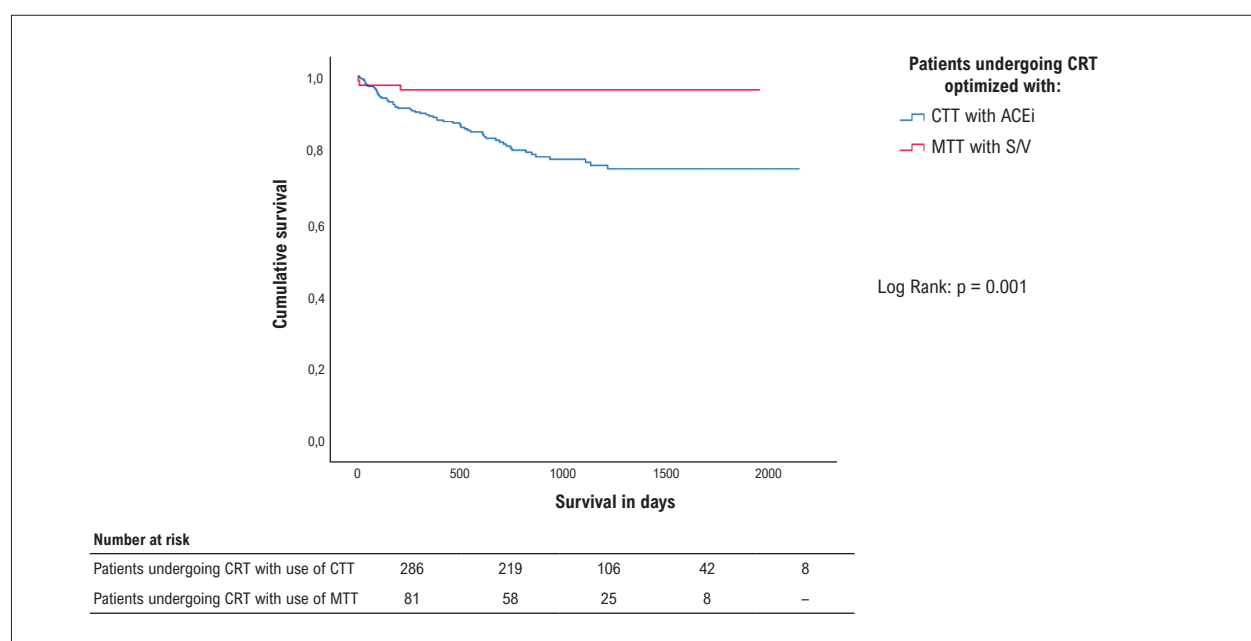


Figure 1 – Kaplan-Meier survival curve of patients undergoing CRT, comparing CTT with ACEi versus MTT with S/V. ACEi: angiotensin-converting enzyme inhibitors; CRT: cardiac resynchronization therapy; CTT: conventional triple therapy; MTT: modern triple therapy; S/V: sacubitril/valsartan.

Table 2 – Univariate and multivariate analysis of all-cause mortality among patients undergoing CRT implantation, according to the therapy used

Variable	HR (95% CI) – Univariate analysis	p-value	HR (95% CI) – Multivariate analysis	p-value
On CTT	1.27 (1.17–1.39)	<0.001	5.83 (1.81–18.70)	0.003
On MTT	0.18 (0.06–0.58)	<0.001	0.71 (0.44–0.67)	0.002
NYHA class II	0.61 (0.38–0.97)	0.030	—	—
Chagas disease etiology	1.81 (1.37–2.41)	<0.001	—	—
Myocarditis	0.29 (0.09–0.91)	0.017	—	—
AF	2.30 (1.52–3.49)	<0.001	—	—
Induced LBBB (upgrade)	1.58 (1.03–2.42)	0.046	—	—
Native LBBB	0.62 (0.45–0.86)	0.001	—	—
No LBBB	1.47 (0.94–2.31)	0.124	—	—
MAGGIC score	1.33 (1.01–1.97)	0.005	—	—
LVEF	1.14 (0.84–1.85)	0.235	—	—

AF: atrial fibrillation; CRT: cardiac resynchronization therapy; CTT: conventional triple therapy; MTT: modern triple therapy; NYHA: New York Heart Association; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure; —: Variable not included in the multivariate model.

S/V, only 18 (24%) were receiving the full dose (200 mg/day), while most were on intermediate (100 mg/day in 35 patients) or initial doses (50 mg/day in 22 patients). Between the 6th and 12th month of follow-up, among the 73 patients who remained on S/V, only 16 (21.9%) maintained the 200 mg/day dose; 42 (57.5%) were using 100 mg/day, and 15 (20.5%) were using 50 mg/day. These data suggest

that even at submaximal doses, MTT was associated with better outcomes, indicating clinical benefit even without full dose optimization. On the other hand, the findings reflect real-world challenges in achieving the target dose, underscoring the need for strategies to enable gradual and safe titration of ARNi whenever possible, to maximize its therapeutic effects.

A study that specifically evaluated eligibility for S/V use in patients with implantable devices found that a significant proportion (43% to 72%) of patients would be eligible for switching from an ACEi to S/V. Due to symptom progression (NYHA class IV), approximately half (17% to 32%) of patients remained eligible for MTT. Additionally, 18% of patients developed a new indication for ARNi during follow-up, highlighting the importance of periodically reassessing drug therapy before and after device implantation.¹⁸

In addition to ARNi, current guidelines also recommend the use of SGLT2 inhibitors, whose combination has been shown to further reduce morbidity and mortality in patients with HFrEF.^{3,4} Recently updated guidelines from the American College of Cardiology and the Canadian Cardiovascular Society have endorsed the so-called quadruple therapy (ARNi, beta-blocker, mineralocorticoid receptor antagonist, and SGLT2i).^{3,6,19-21} However, in the clinical trials that demonstrated the efficacy of these drugs, few patients had indications for CRT. Therefore, there is no robust evidence to support the mandatory use of these medications before considering CRT.

Despite efforts to minimize bias, there are inherent limitations associated with the observational and single-center design of this study, which may compromise its external validity. Additionally, this was a non-randomized study with a convenience sample, although it included a significant number of patients with similar clinical characteristics across groups. Another relevant limitation is temporal bias, as it was not possible to record the duration of CTT or MTT use prior to study enrollment.

Finally, the lower all-cause mortality observed among HFrEF patients receiving MTT compared to those receiving CTT suggests a potential benefit from including ARNi as part of optimized therapy in this population. However, it is essential to highlight that this was an observational, single-center, and nonrandomized study, and therefore subject to various sources of bias. As such, the findings should be interpreted with caution, and further studies using more robust methodologies are needed to definitively confirm the impact of this therapeutic strategy. Maintaining optimized

therapy — including ARNi, when indicated — even after CRT implantation, may represent a beneficial clinical approach. Nevertheless, its application should be individualized and based on careful case-by-case assessment.

Conclusion

Early, sustained use of MTT with S/V was associated with a significant reduction in mortality risk among HFrEF patients undergoing CRT implantation.

Author Contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Passos LCS, Carvalho W, Cafezeiro CRF; Analysis and interpretation of the data: Barros-Pereira JP, Tapioca FPM, Dourado GP, Figueiredo CS; Statistical analysis: Cafezeiro CRF; Critical revision of the manuscript for content: Passos LCS, Cafezeiro CRF, Tapioca FPM, Dourado GP, Figueiredo CS.

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 study was approved by the Ethics Committee of the Hospital Ana Nery under the protocol number 5.825.148. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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