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ORIGINAL RESEARCH

Cardiac Resynchronization Therapy, Remodeling, and Outcome in Patients With Amyloid Transthyretin Cardiomyopathy

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BACKGROUND: Transthyretin amyloid cardiomyopathy (ATTR-CM) has a specific pathophysiology, with myocardial stiffening and systolic dysfunction only in advanced stages. We aimed to investigate the response to cardiac resynchronization therapy (CRT) in ATTR-CM compared with heart failure.

METHODS: In this multicenter, observational study, patients with ATTR-CM receiving CRT (n=101) were matched to patients without amyloid cardiomyopathy by sex, age, and implantation type (CRT with versus without defibrillator versus conduction system pacing, upgrade versus first implant). We evaluated changes in QRS duration and echocardiographic parameters following CRT implantation and at the most recent available assessments. The study end points were all-cause death alone or combined with heart failure hospitalization.

RESULTS: Patients with ATTR-CM (median age, 76 [interquartile range, 72–83] years, 98% men, left ventricular (LV) ejection fraction 30% [26–33]) showed greater QRS shortening after CRT implantation (P=0.012), but not after a median of around 1 year (P=0.152). There were no significant differences in the absolute LV ejection fraction changes immediately after implantation (+7 [+2/+10] versus +3 [0/+9] units; P=0.124), or to the last echo (P=0.796), which was performed after 1.3 years in patients with ATTR-CM and 2.9 years in patients without amyloid cardiomyopathy. Patients with ATTR-CM had a shorter survival than controls (P<0.001 for both end points). Patients with ATTR-CM experiencing an early improvement in LV ejection fraction had a longer survival (log-rank, 4.3; P=0.038).

CONCLUSIONS: Following CRT implantation, patients with ATTR-CM show QRS narrowing and improvement in LV ejection fraction, not different from patients without amyloid cardiomyopathy. Early favorable LV remodeling seems to be associated with a lower risk of all-cause death.

Key Words: cardiac amyloidosis ■ cardiac resynchronization therapy ■ conduction system pacing ■ CRT ■ outcome ■ remodeling ■ transthyretin

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CLINICAL PERSPECTIVE

What Is New?

- In a multicenter matched cohort of 101 patients with transthyretin amyloid cardiomyopathy undergoing cardiac resynchronization therapy, early QRS narrowing was greater and left ventricular ejection fraction improvement was comparable to nonamyloid heart failure, with longer-term remodeling converging between groups.

What Are the Clinical Implications?

- Cardiac resynchronization therapy should be offered to eligible patients with transthyretin amyloid cardiomyopathy, and an early postimplant rise in left ventricular ejection fraction can aid risk stratification because any early increase was associated with lower all-cause death.

Nonstandard Abbreviations and Acronyms

APOLLO-B	A Study to Evaluate the Efficacy and Safety of Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy
ATTR	amyloid transthyretin
ATTR-CM	transthyretin amyloid cardiomyopathy
CRT	cardiac resynchronization therapy
CSP	conduction system pacing
E/e'	ratio of early transmitral Doppler velocity to early diastolic mitral annular velocity
ENDEAVOUR	Phase 3 Multicenter Study of Revusiran in Patients With Transthyretin Mediated Familial Amyloidotic Cardiomyopathy

Amyloid transthyretin (ATTR) amyloidosis is caused by extracellular deposition of misfolded transthyretin.[1] The disease manifests as wild-type ATTR, attributed to an age-related failure of mechanisms of protein homeostasis, or variant ATTR, associated with destabilizing genetic mutations. Transthyretin amyloid cardiomyopathy (ATTR-CM) is due to amyloid deposition leading to structural and functional myocardial changes, including extracellular matrix expansion, progressive diastolic dysfunction, which may progress to systolic dysfunction.[2] Conduction disturbances in the atrioventricular node and along the bundle branches are also common.[3]

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure (HF) with reduced ejection fraction and a wide QRS, improving survival, reducing hospitalizations, and reversing adverse remodeling.[4] The conclusions about CRT efficacy in HF with reduced ejection fraction cannot be readily translated to the ATTR-CM setting given the peculiar pathophysiology of the latter condition, with prominent ventricular stiffness. Existing evidence on CRT in ATTR-CM is limited. In a retrospective study on 30 patients with amyloid cardiomyopathy, Donnellan et al observed improved survival in patients with CRT as compared with a heterogeneous population who did not receive a CRT device.[5] A multicenter study by Fischer et al involving 47 patients with amyloid cardiomyopathy reported lower CRT response rates and worse outcomes compared with a propensity-matched cohort of patients with dilated cardiomyopathy.[6] Interpretation of these findings is challenging by the inclusion of patients with amyloid light-chain cardiomyopathy and the lack of sex matching, as women with HF with reduced ejection fraction respond better to CRT.[7] Additional considerations, such as allowing a left ventricular ejection fraction (LVEF) up to 49%, a relatively small study population, and heterogeneity between patients with ATTR-CM and controls, further limit the ability to draw firm conclusions. Given the lack of strong evidence, we investigated the effects of CRT on cardiac remodeling, function, and outcomes in ATTR-CM.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We evaluated 101 consecutive patients with a definite diagnosis of ATTR-CM who received CRT on the basis of standard indications (wide QRS and LVEF ≤35%). Patient data were provided by the following centers: Columbia University, College of Physicians and Surgeons (New York, NY; n=26); Mayo Clinic (Rochester, MN) and Mayo Clinic Hospital (Phoenix, AZ; n=25); Fondazione Toscana Gabriele Monasterio (Pisa, Italy; n=14); Oregon Health and Science University Medical Group (Portland, OR; n=12); University Hospitals of Brescia (n=6), Florence (n=3), Bologna (n=3), Ferrara (n=2), Trieste (n=2), and Bari, Italy (n=2); Policlinico Umberto I (Rome, Italy; n=3); Ospedale Niguarda (Milan, Italy; n=2); and Sant'Andrea University Hospital (Rome, Italy; n=1). ATTR-CM was diagnosed by tissue biopsy before 2016 or following the noninvasive diagnostic algorithm afterward.[8]

Controls were identified among all patients with HF undergoing CRT implantation at 3 institutions (Fondazione Toscana Gabriele Monasterio, University

Hospitals of Brescia and Trieste) on the basis of standard indications. Controls were selected among individuals without a diagnosis of amyloid cardiomyopathy (either before or after CRT implantation), and with sufficient data in the electronic health records at the time of CRT implantation to check that they did not have left ventricular wall thickness ≥12 plus at least 1 red flag (which would have required a diagnostic workup for amyloid cardiomyopathy).[9] A control was selected for each patient with ATTR-CM to achieve a perfect match of sex, device type (CRT with defibrillation versus pacing alone versus conduction system pacing [CSP]), implant status (first implant versus upgrade), and age at implant. Patients with ATTR-CM and controls were not matched for the year of implantation, but controls were selected among those receiving a CRT during the same time span than patients with ATTR-CM.

All participants in the study provided informed consent for the use of their data for research purposes. The retrospective analysis was approved by an institutional review board/ethics committee at all participating centers.

Data Collection

Demographic data, wild-type or variant ATTR-CM, device type, site of LV pacing, percentage of biventricular pacing at remote controls, electrocardiographic and echocardiographic variables, laboratory examinations (estimated glomerular filtration rate and NT-proBNP [N-terminal pro-B-type natriuretic peptide]), therapy with tafamidis or experimental therapies for ATTR-CM, and conventional HF therapies were retrieved from the electronic health records. The ECG performed on admission and on discharge and the last ECG available during follow-up were considered. Absolute and percentage changes in QRS duration were examined. The echocardiograms performed on admission and within 90 days after discharge and the last echocardiogram available were considered assessing changes in LVEF, ratio of early transmitral Doppler velocity to early diastolic mitral annular velocity (E/e'), tricuspid annular plane systolic excursion, and systolic pulmonary artery pressure.

Management and Follow-Up

Therapy and follow-up protocols were determined at the discretion of the referring physicians. All follow-up durations were calculated from the date of device implantation. The primary end point was all-cause death, and the secondary end point was the composite of all-cause death or HF hospitalization. End point data were gathered from electronic health records or through phone contact with patients, family members, or general practitioners.

Statistical Analysis

Analyses were performed with SPSS Statistics version 24 (IBM, Armonk, NY) and Python version 3.x (packages: statsmodels, lifelines, pandas, matplotlib; Python Software Foundation, Wilmington, DE). Categorical variables are reported as counts (percentages) and compared with the χ^2 test. Continuous variables were assessed with the Shapiro–Wilk test and are presented as medians with interquartile ranges; between-group comparisons used the Mann–Whitney *U* test. Time-to-event outcomes were analyzed with Kaplan–Meier methods and the log-rank test. Associations between periprocedural remodeling markers and outcomes were evaluated with Cox proportional hazards models. Two multivariable Cox models were prespecified to assess independent effects of remodeling: (1) absolute changes in LVEF, absolute change in E/e', and change in mitral regurgitation grade; and (2) percentage changes in LVEF, percentage change in E/e', and change in mitral regurgitation grade. Proportional hazards assumptions were checked by visual inspection of log–log plots and Schoenfeld-type diagnostics when applicable. Subgroup analyses were conducted for first implant versus upgrade, lateral left ventricular lead position versus other positions, presence versus absence of left bundle-branch block at baseline, presence versus absence of atrial fibrillation (AF) at baseline, and tafamidis exposure. To assess whether the association between remodeling markers and death differed by patient group, we fitted pooled Cox models including the main effects of the standardized marker and group (ATTR-CM versus patients without amyloid cardiomyopathy) and their interaction (marker*group). From these models we report the interaction *P* value and group-specific hazard ratios (HRs) with their 95% CIs. Two-sided $P<0.05$ was considered statistically significant.

RESULTS

Study Population: Baseline Characteristics and Follow-Up

The main patient characteristics at the time of implantation are reported in Table 1. Patients with ATTR-CM had a median age of 76 (interquartile range [IQR], 72–83) years, were almost exclusively men (98%), and had wild-type disease in 89% of cases. Median LVEF was 30% (IQR, 26%–33%), and the median NT-proBNP value was 3878 (IQR, 2575–7525) ng/L. Thirty percent of patients with ATTR-CM were receiving tafamidis, 47% β blockers, 47% angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor/neprilysin inhibitor, and 41% mineralocorticoid receptor antagonists, while 92% were taking loop diuretics. Two patients were enrolled in a clinical trial at the time of

Table 1. Patients With ATTR-CM or Without Amyloid Cardiomyopathy: Baseline Characteristics

	Patients with ATTR-CM	Patients without amyloid cardiomyopathy	
	n=101	n=101	*P* value
Male sex, n (%)	99 (98)	99 (98)	…
Age, y	76 (72–83)	76 (72–83)	…
Variant ATTR, n (%)	11 (11)	…	…
Time from diagnosis of ATTR, y	1.1 (0–2.8)	…	…
History of AF, n (%)	60 (59)	62 (62)	0.840
LVEF, %	30 (26–33)	32 (26–35)	0.120
NT-proBNP, ng/L	3878 (2575–7525)	2132 (1045–4318)	0.001*
eGFR, mL/min per 1.73 m^2	52 (39–61)	54 (36–68)	0.313
NAC stage 1/2/3, n (%)	18/13/38 (26/19/55)	…	…
High-sensitivity troponin T, ng/L	76 (42–111)	22 (15–34)	<0.001*
Therapies			
Tafamidis, n (%)	30 (30)	…	…
β blockers, n (%)	41 (47)	81 (81)	<0.001*
ACEi/ARB/ARNI, n (%)	47 (47)	71 (72)	0.001*
MRA, n (%)	41 (41)	46 (47)	0.381
SGLT2i, n (%)	10 (10)	11 (11)	0.888
Loop diuretics, n (%)	93 (92)	75 (74)	<0.001*
ECG			
Sinus rhythm, n (%)	44 (44)	56 (55)	0.136
AF/atrial flutter/tachycardia, n (%)	46 (46)	48 (48)	0.784
Paced rhythm, n (%)	20 (20)	23 (23)	0.595
Heart rate, bpm	70 (60–81)	65 (60–73)	0.056
QRS duration, ms	166 (141–180)	154 (126–175)	0.103
Left bundle branch block, n (%)	66 (65)	71 (70)	0.764
Left anterior hemiblock, n (%)	14 (14)	15 (15)	0.981
Right bundle branch block, n (%)	21 (21)	15 (15)	0.112

As specified in the Methods section, each patient without amyloid cardiomyopathy was selected to have the same sex, device type, implant status (first implant vs upgrade), and age at implant of a patient with ATTR-CM.

ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis cardiomyopathy; CRT, cardiac resynchronization therapy; CSP, conduction system pacing; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NAC, National Amyloidosis Centre; and NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SGLT2i, sodium–glucose cotransporter 2 inhibitor.

*Significant *P* values.

implantation (ENDEAVOUR [Phase 3 Multicenter Study of Revusiran in Patients With Transthyretin Mediated Familial Amyloidotic Cardiomyopathy]; NCT02319005). As expected, patients with ATTR-CM had higher cardiac biomarker levels and were less often on β blockers and angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or angiotensin receptor/neprilysin inhibitor (Table 1).

Patients with ATTR-CM received CRT implantation a median of 13 (IQR, 2–34) months after diagnosis. During follow-up after CRT implantation, 48 patients with ATTR-CM (57% of those with available data) received tafamidis, and 3 patients were enrolled in clinical trials: APOLLO-B (A Study to Evaluate the Efficacy and Safety of Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy), n=2; ENDEAVOUR, n=1. Forty-two patients with ATTR-CM (42%) died from any cause over a 2.9 (IQR, 1.7–4.8)-year follow-up, and 60 (61%) died or were hospitalized for HF over a 1.7 (IQR, 1.0–3.5)-year period. In the group of patients without amyloid cardiomyopathy, 20 (20%) died over 3.3 (IQR, 1.4–6.1) years, and 28 (34%) died or were hospitalized for HF during a 2.7 (IQR, 0.8–5.1)-year follow-up. Therefore, patients with ATTR-CM had a shorter survival than those without amyloid cardiomyopathy (*P*<0.001 for both end points) (Figure S1). Among patients with ATTR-CM, there was no significant difference in survival between patients with CRT with defibrillation, CRT with pacing alone or CSP (*P*=0.372).

Baseline ECG and Device Features

On the ECG recorded at the time of admission, no significant differences emerged between patients with ATTR-CM and those without amyloid cardiomyopathy (Table 1).

Among patients with ATTR-CM or those without amyloid cardiomyopathy, 82 (49%) underwent CRT with defibrillation implantation, 78 (47%) CRT with pacing alone implantation, and 7 (4%) CSP implantation. Furthermore, 40 patients in each group (24%) underwent an upgrade of a previously implanted device.

Implantation was successfully completed in all patients and all controls. Catether position was reported as lateral in 66% of patients and 63% of controls, posterior in 2% of patients and 1% of controls, and posterolateral in 22% of patients and 32% of controls (*P* for comparison=0.367). No complications were reported that would have required a repeat interventional procedure, surgery, or a significant prolongation of hospital stay. The percentage of biventricular pacing at the 3-month follow-up was 98% (IQR, 96%–99%) in patients with ATTR-CM and 97% (IQR, 94%–99%) in patients without amyloid cardiomyopathy (*P*=0.661).

Electrical Remodeling

When comparing the pre- and postprocedural ECGs, the median QRS duration changed from 166 (IQR, 141–180) ms to 145 (IQR, 114–172) ms. The median absolute change was –12 (IQR, 43/+7) ms, and the median percentage change was –8% (–26%/+6%). Among controls, the median QRS duration changed from 154 (IQR, 126–175) ms to 146 (IQR, 135–170) ms. The median absolute change was –1 (–17/+24) ms, and the median percentage change was –1% (–11/+17). The reduction in QRS duration was greater in patients with ATTR-CM than patients without amyloid cardiomyopathy (absolute change, *P*=0.012; percentage change, *P*=0.009) (Figure 1).

When excluding upgrading procedures, patients with ATTR-CM showed a greater absolute and percentage reduction in QRS duration (*P*=0.017 and *P*=0.010, respectively). Conversely, there were no differences based on the presence or absence of left bundle-branch block (*P*=0.429 and *P*=0.402, respectively), or AF at the time of implantation (*P*=0.771 and *P*=0.801, respectively). We also did not observe any difference when stratifying patients according to the tafamidis exposure (before versus after implant versus never; *P*=0.534). Absolute changes in QRS in the different subgroups are reported in Figure S2.

Between the implantation date and the last available ECG, 1.2 (IQR, 0.3–3.1) years elapsed in the group of patients with ATTR-CM and 0.9 (IQR, 0.4–2.5) years in the group of patients without amyloid cardiomyopathy (*P*=0.853). Among patients with ATTR-CM, the absolute and percentage changes in QRS duration were +2 ms (–32/+18) and +1% (–20/+11). Among patients without amyloid cardiomyopathy, the absolute and percentage changes in QRS duration were +8 ms (–23/+48) and +5% (–13/+37). The differences between patients with ATTR-CM and those without amyloid cardiomyopathy were not significant (*P*=0.152 and *P*=0.130, respectively) (Figure 1).

We then repeated the subgroup analyses considering the first versus last ECG. Among patients, no differences emerged between those undergoing an upgrading or not, with a catheter in the lateral position versus in any other positions, with or without left bundle-branch block at baseline, AF, or tafamidis exposure. Absolute changes in QRS in the different subgroups are reported in Figure S3.

Echocardiographic Remodeling

Between implantation and the first postimplantation echocardiogram, 12 (IQR, 5–45) days elapsed in patients with ATTR-CM and 8 (IQR, 3–38) days in patients without amyloid cardiomyopathy (*P*=0.554). Between implantation and the last available echocardiogram, 1.3 (IQR, 0.5–2.9) years elapsed in the group of patients with ATTR-CM (n=69) and 1.9 (IQR, 0.7–3.3) years in the group of patients without amyloid cardiomyopathy (*P*=0.398).

Postprocedural recovery in LVEF did not differ significantly in the 1 groups (+7 units [+2/+10] versus +3 [0/+9], *P*=0.124; +18% [+6/+37] versus +9% [0/+27], *P*=0.119) (Table 2, Figure 2). Nonetheless, no significant difference was observed when comparing the last echocardiogram with the preimplant echocardiogram. LVEF increased by 5 units in both patients with ATTR-CM and those without amyloid cardiomyopathy (*P*=0.796) and by 16% versus 17%, respectively (*P*=0.851) (Table 2, Figure 2).

Subgroup analyses (first implant versus upgrading, catheter in the lateral position versus in any other positions, patients with versus without left bundle-branch block or AF, or tafamidis exposure) did not reveal any significant difference. Absolute changes in LVEF in the different subgroups are reported in Figures S4 and S5.

Prognostic Value of Periprocedural Changes in QRS Duration and LVEF

As stated above, patients with ATTR-CM had a worse prognosis than patients without amyloid cardiomyopathy. Periprocedural changes in LVEF, E/e', and mitral regurgitation grade predicted the risk of all-cause death in patients with ATTR-CM (Table 3). Absolute changes in LVEF were the strongest predictors of all-cause death (HR, 0.81 [95% CI, 0.69–0.96]; *P*=0.012) in univariable analysis. Absolute changes in LVEF also predicted all-cause death independent of absolute changes in E/e' and mitral regurgitation grade (HR, 0.89 [95% CI,

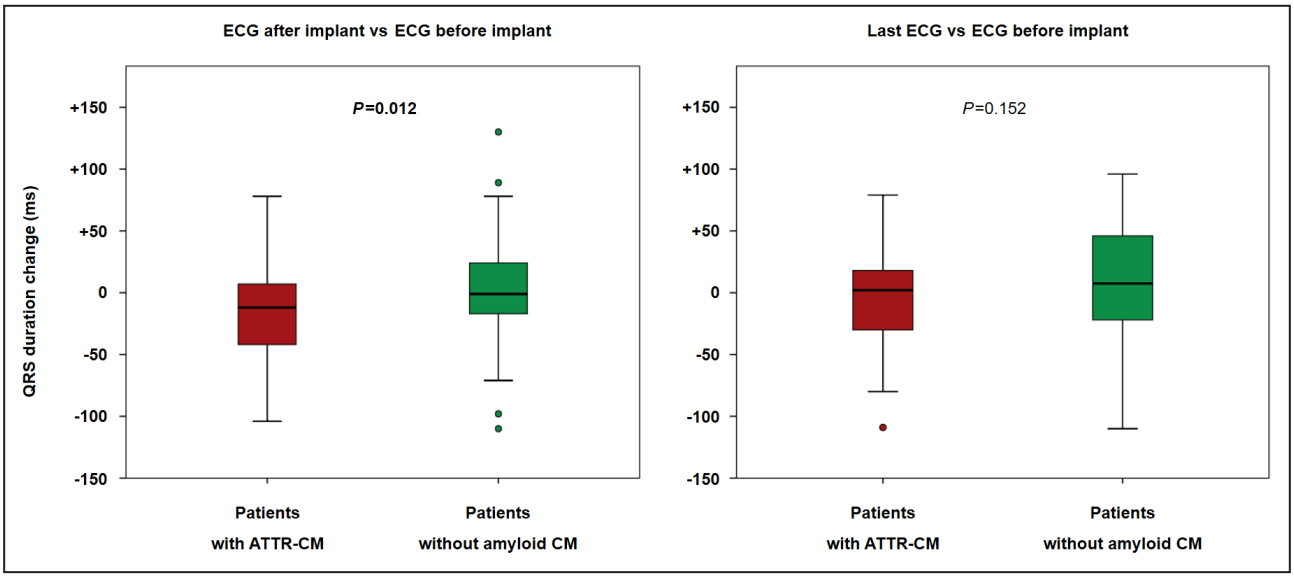

Figure 1. Changes in QRS duration in patients with ATTR-CM and patients without amyloid cardiomyopathy.
The first postimplantation ECG was compared with the baseline ECG (left); then the last available ECG was compared with the baseline ECG (right). For the time intervals between the examinations, see text. ATTR-CM indicates transthyretin amyloid cardiomyopathy; and CM, cardiomyopathy.

0.80–0.99]; *P*=0.047), whereas percentage changes in LVEF did not predict all-cause death independent of percentage changes in E/e' and (absolute) changes in mitral regurgitation grade (*P*=0.069).

In a pooled Cox model including absolute LVEF changes (standardized), patient group, and their interaction, the HR per 1-SD increase in ΔLVEF was 0.33 (95% CI, 0.13–0.83) in ATTR-CM and 0.81 (95% CI, 0.20–3.35) in patients without amyloid cardiomyopathy (*P* for interaction=0.303). Thus, higher periprocedural improvement in LVEF was associated with a lower mortality rate in ATTR-CM, with no statistically significant difference between groups.

The prognostic value of absolute LVEF changes for all-cause death did not change significantly across subgroups (all *P* for interaction >0.05), in line with the independent prognostic value of absolute changes in LVEF (Figure S6). Finally, patients with ATTR-CM experiencing any increase in LVEF had a longer survival free from all-cause death (log-rank, 4.3; *P*=0.038; Figure S7).

Table 2. Changes in the Echocardiographic Parameters

		Echocardiogram after implant vs preimplant echocardiogram			Last echocardiogram vs preimplant echocardiogram		
		Patients with ATTR-CM	Patients without amyloid cardiomyopathy	*P* value	Patients with ATTR-CM	Patients without amyloid cardiomyopathy	*P* value
LVEF change	Absolute, %	+7 (+2/+10)	+3 (0/+9)	0.124	+5 (0/+11)	+5 (0/+14)	0.796
	Percentage	+18 (+6/+37)	+9 (0/+27)	0.119	+16 (0/+44)	+17 (–1/+47)	0.851
E/e' change	Absolute	–1 (–6/+1)	0 (–3/+2)	0.077	–2 (–5/+6)	–1 (–4/+3)	0.723
	Percentage	–6 (–33/+2)	–3 (–10/+15)	0.063	–7 (–22/+18)	–7 (–24/+19)	0.865
Mitral regurgitation grade	Absolute	–1 (–1/0)	0 (–1/0)	0.352	0 (–1/0)	0 (–1/0)	0.107
TAPSE change	Absolute, mm	+1 (0/+1)	0 (–1/0)	0.100	0 (–2/+3)	–2 (–4/+1)	0.085
	Percentage	+2 (0/+9)	0 (–5/0)	0.142	0 (–10/+30)	–9 (–21/+7)	0.097
sPAP change	Absolute, mm Hg	–5 (–17/–1)	+2 (–8/+12)	0.138	–4 (–16/+3)	–3 (–13/+5)	0.433
	Percentage	–17 (–35/–3)	+3 (–16/+25)	0.138	–9 (–28/+9)	–7 (–27/+13)	0.571

ATTR-CM indicates amyloid transthyretin cardiomyopathy; E/e', ratio of early transmitral Doppler velocity to early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; and TAPSE, tricuspid annular plane systolic excursion.

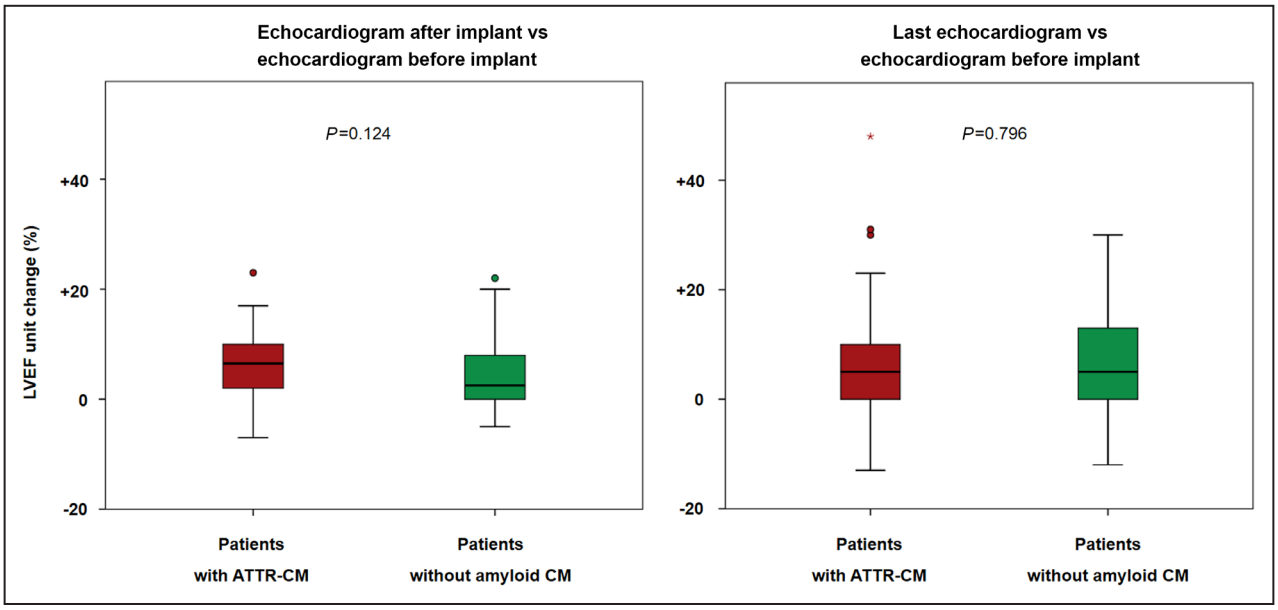

Figure 2. Changes in LVEF in patients with ATTR-CM and patients without amyloid cardiomyopathy.
Absolute changes in LVEF were evaluated between the first postimplant echocardiogram and the baseline echocardiogram (left) and between the last available echocardiogram and the baseline echo (right). For the time intervals between the examinations, see text. ATTR-CM indicates transthyretin amyloid cardiomyopathy; CM, cardiomyopathy; and LVEF, left ventricular ejection fraction.

DISCUSSION

This study provides a detailed analysis of the response to CRT in patients with ATTR-CM, as well as how this response evolves over time. We report that patients with ATTR-CM demonstrate a good response to CRT, with reduction in QRS duration that are even more pronounced than those seen in patients without amyloid cardiomyopathy and a similar response in terms of echocardiographic parameters. The response to CRT becomes similar over the longer term. The survival of patients with ATTR-CM remains much shorter than patients without amyloid cardiomyopathy. Among patients with ATTR-CM, a greater early recovery in LVEF predicts a better outcome, with a longer survival if patients experience any increase in LVEF.

Ideally, evaluating the efficacy of CRT in ATTR-CM would require a randomized controlled trial comparing patients who receive the device with those who do not. However, such a trial is unlikely to be conducted due to the rarity of ATTR-CM, competitive enrollment with other randomized controlled trials, and the common practice of extending recommendations about HF care to the amyloidosis setting. Consequently, retrospective studies with accurate matching between groups are essential. We assembled the largest cohort of patients with ATTR-CM who received a CRT device and matched them on the basis of sex, age, and type of device to patients with a reasonably low likelihood of amyloid cardiomyopathy. These last patients were recruited at referral centers from individuals without clinical "red flags," minimizing the likelihood of undiagnosed amyloid cardiomyopathy. In contrast with a previous small study including patients with LVEF <50%,[6] we used the traditional LVEF 35% threshold.[10] We assessed the response to CRT in terms of QRS narrowing and changes in key echocardiographic parameters. We also evaluated 2 hard end points, namely, all-cause death and the combined outcome of all-cause death or HF hospitalization.

Our study design ensured close matching for sex, age, device category (CRT with defibrillation /CRT with pacing alone /CSP) and implant status, so that any contrasts primarily reflect the underlying myocardial substrate rather than demographic or procedural biases. At baseline, both cohorts fulfilled conventional CRT criteria, yet the ATTR-CM group displayed hallmarks of more advanced or systemic disease (higher NT-proBNP concentrations and less frequent use of neurohormonal therapies). Electrical characteristics were broadly similar, with no significant differences in QRS duration and even in the prevalence of AF. This last finding likely reflects the impact of age, structural atrial remodeling and conduction disease conferring AF rates similar to those observed in ATTR-CM, thereby obscuring any additional arrhythmogenic impact of atrial amyloid infiltration.

Despite theoretical concerns that myocardial stiffness might diminish the response to CRT, patients with ATTR-CM demonstrated a response comparable with that of patients without amyloid cardiomyopathy. Specifically, patients with ATTR-CM experienced

Table 3. Prognostic Value of Periprocedural Changes in QRS Duration and Echocardiographic Parameters

			Patients with ATTR-CM			Patients without amyloid cardiomyopathy		
			HR	95% CI	*P* value	HR	95% CI	*P* value
All-cause death	QRS change	Absolute, %	1.00	0.99–1.01	0.679	1.00	0.99–1.02	0.645
		Percentage	1.00	0.98–1.01	0.673	1.00	0.99–1.01	0.875
	LVEF change	Absolute, %	0.81	0.69–0.96	0.012*	0.97	0.78–1.20	0.755
		Percentage	0.95	0.91–0.99	0.045*	0.86	0.63–1.03	0.864
	E/e' change	Absolute	1.38	1.02–1.88	0.037*	1.15	0.89–1.65	0.469
		Percentage	1.07	1.00–1.42	0.038*	0.98	0.94–1.03	0.453
	Mitral regurgitation grade	Absolute	…	…	0.029*	…	…	0.567
	TAPSE change	Absolute, mm	0.35	0.11–1.15	0.084	0.79	0.59–1.20	0.611
		Percentage	0.90	0.79–1.04	0.141	0.95	0.75–1.24	0.562
	sPAP change	Absolute, mm Hg	1.00	0.95–1.06	0.870	0.97	0.88–1.07	0.525
		Percentage	0.99	0.97–1.03	0.991	0.98	0.93–1.03	0.405
All-cause death or HF hospitalization	QRS change	Absolute, %	1.00	0.99–1.01	0.918	1.00	0.99–1.02	0.847
		Percentage	1.00	0.99–1.01	0.745	1.01	0.99–1.02	0.959
	LVEF change	Absolute, %	1.02	0.92–1.14	0.705	0.96	0.92–1.01	0.170
		Percentage	1.00	0.99–1.02	0.558	0.99	0.98–1.00	0.177
	E/e' change	Absolute	0.95	0.72–1.25	0.705	0.94	0.70–1.17	0.678
		Percentage	0.99	0.94–1.04	0.558	0.98	0.84–1.10	0.790
	Mitral regurgitation grade	Absolute	…	…	0.299	…	…	0.419
	TAPSE change	Absolute, mm	1.09	0.80–1.48	0.585	1.02	0.93–1.11	0.506
		Percentage	1.01	0.98–1.05	0.579	1.00	0.99–1.02	0.448
	sPAP change	Absolute, mm Hg	0.98	0.93–1.04	0.445	1.03	0.99–1.07	0.722
		Percentage	0.96	0.93–1.02	0.591	1.00	1.00–1.03	0.987

Univariable Cox regression analysis. HR and 95% CI values are reported for all the variables, except for the categorical variables "changes in mitral regurgitation grade."

ATTR-CM indicates amyloid transthyretin cardiomyopathy; E/e', ratio of early transmitral Doppler velocity to early diastolic mitral annular velocity; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; and TAPSE, tricuspid annular plane systolic excursion.

*Significant *P* values.

a reduction in QRS duration of –12 ms (–8% relative to the preimplant ECG), which was even greater than that observed in patients without amyloid cardiomyopathy (*P*=0.012 for the absolute change, *P*=0.009 for the percentage change). This difference likely reflects a slightly longer baseline QRS duration in the ATTR-CM group, although the difference was not statistically significant. "Electrical remodeling" was accompanied, in patients with ATTR-CM, by an increase in LVEF by 7 units, or 18%, as compared with 3 units and +9% in patients without amyloid cardiomyopathy. The strong functional recovery in patients with ATTR-CM is consistent with previous studies, such as Donnellan et al (where LVEF increased from 25%±9% to 36%±13%)[5] and Fischer et al (where the median LVEF rose from 30% to 37%).[6] Over the long term, the response to CRT tends to become similar in patients with ATTR-CM and those without amyloid cardiomyopathy; for example, LVEF increased by 5 units in both groups. Furthermore, patients with ATTR-CM experience significantly shorter survival, likely because they have progressed from diastolic to systolic dysfunction, and are therefore in an advanced disease stage with poor outcome.[11,12] Nonetheless, among patients with ATTR-CM, a greater postprocedural increase in LVEF was associated with better outcome, possibly by identifying patients with some residual functional reserve.

Several limitations must be acknowledged. First, in the absence of randomized data, it would have been better to use a control group of matched patients withATTR-CM with CRT indications who did not get CRT than a non-ATTR-CM control group. Nonetheless, this is not feasible because these patients with ATTR-CM meeting standard criteria undergo CRT implantation. Second, while the amyloid cardiomyopathy population was derived from multiple centers in the United States and Italy, the control group was from Italian centers alone, possibly introducing bias in terms of referral to CRT implantation and management patterns. Furthermore, restricting the control group to patients whose records were detailed enough to rule out red-flag features of amyloid cardiomyopathy could have introduced selection bias. Nonetheless, the risk of such bias is probably limited because referral centers for amyloid cardiomyopathy tend

to systematically screen for these red flags. Additionally, the study population was predominantly men, which is consistent with the known epidemiology of ATTR-CM, but this skewed sex distribution limits the generalizability of our results to women and complicates comparisons with cohorts that have a more balanced sex ratio. Third, the timing of examinations was not standardized, and potentially relevant variables (eg, quality-of-life measures or exercise capacity) were not collected. Fourth, conventional echocardiographic metrics may miss subclinical remodeling detectable by speckle-tracking strain, and changes in global longitudinal strain after CRT hold prognostic value.[13,14] Future studies should then evaluate the echocardiographic response to CRT also as changes in global longitudinal strain. Fifth, many of the ATTR-CM patients received their devices in the pretherapy era, as only 30% were on tafamidis at the time of implantation, although 57% received tafamidis during follow-up. Finally, we did not examine the possible impact of atrioventricular node ablation or a ventricular sense response mechanism in patients with AF.

Despite these possible limitations, our results demonstrate that CRT exerts positive effects on both electrical and structural/functional remodeling in patients with ATTR-CM. These effects appear at least as favorable as those seen in individuals without amyloid cardiomyopathy, although the overall survival remains shorter in the amyloid cardiomyopathy population, likely due to the advanced disease stage.

ARTICLE INFORMATION

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None.

Supplemental Material

Figures S1–S7

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