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RESEARCH LETTER

# Cardiac Resynchronization Therapy for Transthyretin Cardiac Amyloidosis

Eoin Donnellan, MD; Oussama M. Wazni, MD; Mazen Hanna, MD; Mohamed Kanj, MD; Walid I. Saliba, MD; Wael A. Jaber, MD

Transthyretin cardiac amyloidosis (ATTR-CA) is caused by the extracellular deposition of misfolded precursor proteins and represents an increasingly recognized cause of heart failure in older adults.[1] Reduced left ventricular ejection fraction (LVEF) portends a poor prognosis in ATTR-CA.[2] Despite the fact that the role of cardiac resynchronization therapy (CRT) for patients with heart failure with reduced LVEF is well-established, little is known about the efficacy of CRT in ATTR-CA and its use remains controversial.[3] A high burden of right ventricular pacing is associated with adverse outcomes in ATTR-CA.[4] In this study, we investigated the impact of CRT on symptomatic status, cardiac function, and death.

The data that support the findings of this study are available from the corresponding author upon reasonable request. After obtaining consent-exempt approval from our institutional review board, we evaluated 30 consecutive patients with ATTR-CA who underwent CRT implantation and matched them on the basis of age, sex, LVEF, New York Heart Association (NYHA) functional class, and ATTR-CA stage, as defined by the UK National Amyloidosis Staging System,[5] with 30 patients with ATTR-CA who did not receive a CRT device. NYHA functional class and LVEF were assessed at the time of device implant and after 6 months of biventricular pacing. Continuous variables are expressed as mean±SD and compared using ANOVA. Categorical data are presented as percentages and compared using the chi-square test. Cumulative event rates as a function over time were obtained using the Kaplan-Meier method and event curves of different outcomes were compared using the log-rank test. A 2-sided $P<0.05$ was considered statistically significant. Predictors of mortality were assessed using Cox proportional hazards regression models.

Baseline characteristics are shown in the Figure—Panel a. Of the 30 patients with CRT devices, 21 (70%) had CRT-Defibrillator, whereas 9 (30%) had CRT-Pacemaker Before implant, 18 (60%) had left bundle branch block (LBBB), 4 (13%) had right bundle branch block, 4 (13%) had interventricular conduction delay, and 4 (13%) had a narrow QRS complex. Indications for CRT-Defibrillator were: LVEF ≤35%+LBBB with QRS ≥150 milliseconds in 6 (29%); LVEF ≤35%+LBBB with QRS 120 to 150 milliseconds in 9 (43%); LVEF ≤35%+non-LBBB with QRS ≥150 in 2 (9%); and LVEF ≤35%+non-LBBB with QRS 120 to 150 milliseconds in 4 (19%). Indications for CRT-Pacemaker were: post–atrioventricular junction ablation in 6 (67%) and high-grade antrioventricular block in 3 (33%). Among those without devices, 3 (10%) had LVEF ≤35%+LBBB with QRS ≥150 milliseconds; 1 (3%) had LVEF ≤35%+LBBB with QRS 120 to 150 milliseconds; 7 (23%) had LVEF ≤35%+non-LBBB with QRS ≥150 milliseconds; and 4 (13%) had non-LBBB with QRS 120 to 150 milliseconds.

The mean native QRS duration was 147±33 milliseconds. The mean biventricular pacing was 94±9%. Mean LVEF at the time of CRT implant was 33±15%, compared with 38±14% at 6 months ($P<0.001$). In those without devices, mean LVEF at baseline was 34±9% compared with 31±9 at 6 months ($P<0.001$). One further patient in the non-CRT group was started on tafamidis during follow-up. Improvement in LVEF of ≥5% was seen in 15 (50%), 10 (67%) of whom had underlying LBBB, whereas improvement of ≥10% was

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Correspondence to: Wael A. Jaber, MD, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195. E-mail: jaberw@ccf.org

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**a**

| Variable | No CRT (n=30) | CRT (n=30) | p-value |
|---|---|---|---|
| Age (Years) | 76±7 | 76±7 | 0.99 |
| Male Sex | 27 (90%) | 27 (90%) | 0.99 |
| Wild-Type ATTR | 10 (33%) | 10 (33%) | 0.99 |
| ATTR-CA Stage | 2.2±0.7 | 2.1±0.6 | 0.17 |
| NYHA Class | 2.6±0.6 | 2.9±0.7 | 0.7 |
| Native QRS Dutation (msec) | 128±36 | 147±33 | 0.04 |
| Left Bundle Branch Block | 4 (13%) | 18 (60%) | <0.001 |
| Atrial Fibrillation | 23 (77%) | 29 (97%) | 0.03 |
| Obstructive CAD | 9 (30%) | 6 (20%) | 0.28 |
| Beta Blocker | 10 (33%) | 7 (23%) | 0.57 |
| ACE/ARB | 5 (17%) | 1 (3%) | 0.2 |
| Aldosterone Antagonist | 8 (27%) | 10 (33%) | 0.78 |
| Tafamidis | 1 (3%) | 3 (10%) | 0.61 |
| NT-proBNP (pg/mL) | 6954±8840 | 9417±13459 | 0.44 |
| eGFR (ml/min/1.73m$^2$) | 46±15 | 44±14 | 0.59 |
| LV Mass Index (g/m$^2$) | 163±27 | 188±48 | 0.11 |
| Ejection Fraction (%) | 34±9 | 33±15 | 0.73 |

**b**

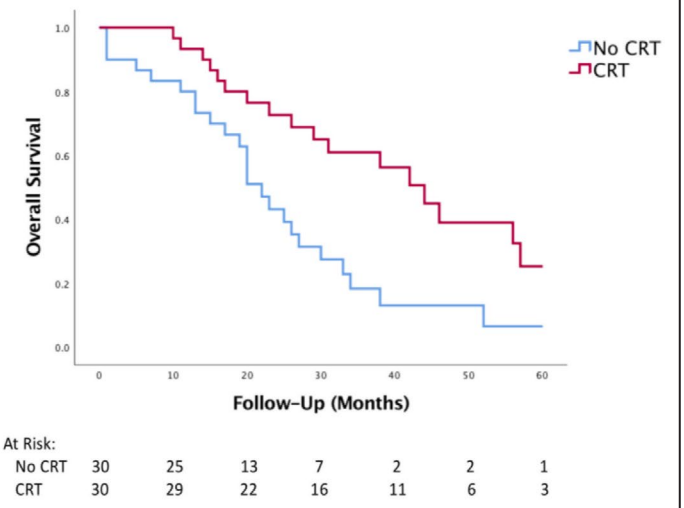


**Figure. Baseline characteristics and impact on survival.**
**A**, Baseline characteristics of patients with and without CRT devices. **B**, Kaplan-Meier curves for overall survival for patients with and without CRT devices. ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; ATTR, transthyretin; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; LV, left ventricle; and NYHA, New York Heart Association.

observed in 10 (33%), and 8 (27%) had an improvement of ≥15%. Worsening LVEF was observed in 10 (33%) patients. At 6 months, heart failure symptoms improved by ≥1 NYHA functional class in 14 (47%), 12 (86%) of whom had LBBB. Worsening NYHA functional class occurred in 8 (27%) patients. During a mean follow-up of 30±24 months, death occurred in 18 (60%) patients with CRT devices, compared with 25 (83%) of those without devices (*P*=0.002; Figure—Panel b). On Cox proportional hazards analyses adjusting for age, LVEF, and NYHA functional class, CRT was associated with improved survival (hazard ratio [HR], 0.39; 95% CI, 0.21–0.74; *P*=0.003), whereas more advanced ATTR-CA stage was associated with increased mortality (HR, 1.8; 95% CI, 1.12–2.86; *P*=0.014).

In this study we have evaluated the efficacy of CRT in ATTR-CA and the impact of CRT on survival. Our main findings were: (1) CRT is associated with improved survival among patients with ATTR-CA; and (2) CRT is associated with improvements in heart failure symptoms and LVEF in ATTR-CA.

Given the poor prognosis of ATTR-CA with a reduced LVEF, the utility of CRT in this population remains clinically controversial and CRT implantation in ATTR-CA is rare. Although the beneficial effects of CRT in appropriately selected patients with reduced LVEF are incontrovertible, the efficacy of biventricular pacing in ATTR-CA has not been studied. Our findings suggest that CRT should be considered in patients with ATTR-CA who meet guideline criteria for CRT implantation. Limitations of our study include its single-center, retrospective nature, and the relatively low number of patients with ATTR-CA undergoing CRT implantation. Furthermore, obstructive CAD was more prevalent in the non-CRT group, and a mixed phenotype comprising both ischemic and nonischemic cardiomyopathy may have been possible. However, we reviewed the technetium pyrophosphate studies for areas of previous infarct. These areas should be easily identifiable as they do not pick up technetium pyrophosphate and this was not evident in any of our cohort. This makes it less likely that regional left ventricular dysfunction was attributable to previous CAD.

## ARTICLE INFORMATION

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### Affiliations

From the Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH.

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### Disclosures

None.

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