Long-Term Survival of Patients With Left Bundle Branch Block Who Are Hypo-Responders to Cardiac Resynchronization Therapy

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Guidelines support cardiac resynchronization therapy with a defibrillator (CRT-D) in mild heart failure (HF) patients with left bundle branch block (LBBB). However, not all patients demonstrate echocardiographic or clinical response to CRT-D. We aimed to evaluate the long-term outcomes of echocardiographic hypo-responders and clinical hypo-responders to CRT-D with LBBB in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy. Five-hundred thirty-four patients with LBBB in the CRT-D arm were followed for 5.6 years (median). Clinical hypo-response was defined as HF event in the first year after CRT-D implantation. Echocardiographic hypo-response was defined as ≤35% reduction (median) in left ventricular end-systolic volume 1 year after CRT-D implantation without evidence of clinical hypo-response. Echocardiographic and clinical response was observed in 257 patients (48%). Two-hundred fifty patients (47%) were echocardiographic hypo-responders and 27 patients (5%) were clinical hypo-responders. Echocardiographic hypo-responders had increased risk of all-cause mortality compared with echocardiographic + clinical responders (hazard ratio [HR] 2.85, 95% confidence interval [CI]: 1.37 to 5.94, p = 0.005). Clinical hypo-responders had increased risk of mortality compared with echocardiographic + clinical responders (HR 7.49, 95% CI: 2.88 to 19.48, p <0.0001) and compared with echocardiographic hypo-responders (HR 2.63, 95% CI: 1.17 to 5.92, p = 0.020). In conclusion, during long-term follow-up, patients with mild HF and LBBB who have echocardiographic hypo-response to CRT, with or without clinical signs of worsening HF, have increased risk of mortality. This study emphasizes the prognostic significance of echocardiographic assessment of left ventricular volume after CRT implantation in LBBB patients with mild HF. **(Am J Cardiol 2017;120:825–830)**

Cardiac resynchronization therapy with a defibrillator (CRT-D) is an established treatment for patients with left bundle branch block (LBBB), mildly symptomatic heart failure (HF), and left ventricular dysfunction.[1–6] However, not all patients with LBBB and mild HF demonstrate echocardiographic or clinical response to CRT-D, and long-term outcomes of hypo-responders to CRT-D have not been well described. Reduction in left ventricular volume after CRT-D implantation has been associated with survival benefit in patients with prolonged QRS duration.[7–13] However, the long-term mortality of echocardiographic hypo-responders and clinical hypo-responders with mild HF has not been thoroughly described or compared previously. The present study was performed in a population of patients with LBBB, mild HF, and left ventricular dysfunction enrolled in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). We aimed to evaluate long-term outcomes of echocardiographic hypo-responders and clinical hypo-responders to CRT-D.

Methods

The design, primary results, and long-term survival data of the MADIT-CRT have been published previously.[1,2] Briefly, MADIT-CRT was designed to determine whether CRT-D would reduce the risk of death or HF events in patients with mild cardiac symptoms, a reduced ejection fraction (EF), and wide QRS complex compared with implantable cardioverter-defibrillator (ICD) therapy. A total of 1,820 patients were enrolled at 110 hospital centers in North America and Europe and randomly assigned in a 3:2 ratio to receive either CRT-D or ICD. The study complied with the Declaration of Helsinki. The protocol was approved by the institutional review board at each of the participating centers. All patients provided written, informed consent. Patients who were ≥21 years of age were enrolled in the study if they had ischemic

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This work (MADIT-CRT study) was supported by an unrestricted research grant from Boston Scientific to the University of Rochester, Rochester, New York, USA.

Clinical Trial Registration: [MADIT-CRT NCT00180271, MADIT-CRT PAR NCT01294449, MADIT-CRT LIFR NCT02060110].

See page 830 for disclosure information.

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0002-9149/
http://dx.doi.org/10.1016/j.amjcard.2017.06.001

cardiomyopathy (New York Heart Association [NYHA] functional class I or II) or nonischemic cardiomyopathy (NYHA class II only), sinus rhythm, an EF ≤0.30, and QRS ≥130 milliseconds. All eligible subjects met guideline indications for ICD therapy. A total of 854 patients participated in post-trial long-term follow-up (median period of 5.6 years). The present study comprises 534 patients with LBBB in the CRT-D arm with at least 1 year of follow-up data and echocardiograms obtained at baseline and 1 year after CRT-D implantation. The primary end point of the present study was death from any cause observed after 1 year of follow-up.

Clinical hypo-response was defined as HF event in the first year after CRT-D implantation. The diagnosis of an HF event, made by physicians aware of the implanted devices, required signs and symptoms consistent with congestive HF that was responsive to intravenous decongestive therapy on an outpatient basis or an augmented decongestive regimen with oral or parenteral medications during an in-hospital stay. Adjudication of the end points was carried out by an independent HF event committee blinded to device implantation information.

Echocardiographic hypo-response was defined as ≤35% reduction in left ventricular end-systolic volume (LVESV) 1 year after CRT-D implantation, without evidence of clinical hypo-response. Thirty-five percent reduction in LVESV was chosen because it was the median value in this cohort. Previous studies have shown that left ventricular reverse remodeling develops within the first year after CRT-D implant, and, therefore, we used reduction in LVESV at 1 year after CRT-D implantation to define echocardiographic response.[14]

Echocardiograms were obtained according to a study-specific protocol at baseline (before device implantation) and at 1 year. Echocardiograms were sent to the echocardiographic core laboratory at Brigham and Women's Hospital, Boston, MA, where they were screened for quality, and left ventricular measurements were made. Echocardiographic parameters were measured according to established American Society of Echocardiography protocols. Left ventricular volumes were measured by the Simpson method of disks in the apical 4- and 2-chamber views and averaged. Left ventricular ejection fractions were calculated according to standard methods. Reproducibility of the primary volumetric measurements was assessed by having the primary observer reanalyze 101 random studies as previously described.[15] The coefficients of variation for left ventricular end-diastolic volume, LVESV, and EF were 5.2%, 6.2%, and 5.5%, respectively.[15]

Demographic characteristics, clinical characteristics, vital signs, other laboratory and diagnostic testing, and medication use were compared between responders and hypo-responders. All continuous variables were reported as mean ± standard deviation. Categorical variables were expressed as number (%). Baseline characteristics were compared using the Kruskal-Wallis test for continuous measurements and chi-square tests for categorical variables, as appropriate. The best subsets procedure was used with the HF or death end point to select variables utilized for multivariate adjustment in the Cox proportional hazards regression models. Additionally, the variables selected by the best subsets procedure also needed to be significant at $p < 0.05$ to be included in the final multivariable model. The baseline measurements used for adjustment were left ventricular EF, previous coronary artery bypass surgery, QRS <150 milliseconds, diastolic blood pressure, and blood urea nitrogen. The Kaplan-Meier method was used for the graphical display of the cumulative probability of all-cause mortality. All analyses were performed using SAS version 9.4 (Cary, NC), statistical tests were 2 sided, and $P < 0.05$ was considered statistically significant.

Results

Five-hundred thirty-four patients with LBBB in the CRT-D arm of MADIT-CRT were followed for 5.6 years (median). Echocardiographic and clinical response was observed in 257 patients (48%). Two-hundred fifty patients (47%) were echocardiographic hypo-responders only. Twenty-seven patients (5%) were clinical hypo-responders. Among clinical hypo-responders, 18 (67%) had ≤35% reduction in LVESV 1 year after CRT-D implantation. Fifty patients (9%) died during long-term follow-up. Table 1 describes baseline characteristics of responders and hypo-responders.

Patients with clinical hypo-response had a significantly higher risk of all-cause mortality compared with patients with echocardiographic hypo-response, or echocardiographic and clinical response (Figure 1). Table 2 further describes outcomes of responders and hypo-responders. Multivariable adjusted analyses showed that echocardiographic hypo-responders had a significantly increased risk of all-cause mortality compared with echocardiographic + clinical responders (Table 3). Clinical hypo-responders had a significantly increased risk of mortality compared with echocardiographic + clinical responders, and compared with echocardiographic hypo-responders.

From baseline to 1 year, the average left ventricular EF increased by 15.7 ± 3.5% in the responders group, 8.3 ± 3.6% in the echo hypo-responders group, and 9.5 ± 5.3% in the clinical hypo-responders group (Figure 2). Responders had a significantly greater reduction in LVESV and significantly greater increase in EF compared with the other 2 groups. Clinical hypo-responders had significantly greater reduction in LVESV and significantly greater increase in EF compared with echocardiographic hypo-responders.

Discussion

In this sub-study of MADIT-CRT, we demonstrated that patients with mild HF with LBBB and echocardiographic or clinical hypo-response to CRT-D at 1 year have an increased risk of subsequent long-term all-cause mortality relative to patients with echocardiographic and clinical response. Clinical hypo-response to CRT-D, defined as the presence of a nonfatal HF event in the first year, carries a higher risk of subsequent long-term all-cause mortality and this finding is expected. However, our study demonstrated that in patients with LBBB with mild HF, echocardiographic hypo-response with or without clinical signs of worsening HF was associated with significantly increased mortality, and this observation indicates the need for repeated assessment of left ventricular volume and function during follow-up of patients with CRT-D with LBBB.

The MADIT-CRT trial included patients with NYHA class I or II HF before CRT-D implantation with low short-term mortality. In this population of patients with only mildly