A Metric for Evaluating the Cardiac Response to Resynchronization Therapy

Yidi Ge, BS[a], Anne-Christine Huth Ruwald, MD[a,b], Valentina Kutyifa, MD, PhD[a], Scott McNitt, MS[a], Slava Polonsky, MS[a], Helmut Klein, MD[a], Ilan Goldenberg, MD[c], Scott D. Solomon, MD[d], Elyse Foster, MD[e], Wojciech Zareba, MD, PhD[a], and Arthur J. Moss, MD[a,*]

We hypothesized that the response to cardiac resynchronization therapy with a defibrillator (CRT-D) in patients with mildly symptomatic heart failure (HF) is more favorable than the commonly referenced figure of 70%. This study involves the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) study population in which paired echocardiograms from baseline and 1-year follow-up were available in 621 implantable cardioverter-defibrillator−treated patients and 749 patients treated with CRT-D. We prespecified CRT-D responders as the patients who at 1-year follow-up had a reduction in left ventricular end-systolic volume (LVESV) that corresponded to the top (best) quintile of LVESV reduction in the implantable cardioverter-defibrillator−treated patients, that is, a ≥17% reduction in LVESV. Using this metric, 88% of patients treated with CRT-D and 91% of the patients treated with CRT-D with left bundle branch block (LBBB) were identified as cardiac resynchronization therapy responders. Landmark multivariate Cox model analyses revealed a significant interaction ($p = 0.038$) involving LVESV (responders vs nonresponders) and LBBB (present vs not present) in risk reduction for HF or death. The interaction finding indicates that cardiac resynchronization therapy responders with LBBB have a significantly lower risk for HF or death (hazard ratio [HR] 0.24) than patients without LBBB (HR 0.62). In the patients treated with CRT-D, LVESV response was associated with reduction in the risk of death (HR 0.20, $p < 0.001$). An increasing percent reduction in LVESV was associated with progressively lower rates of HF or death, a finding consistent with a dose-response relation. In conclusion, approximately 90% of CRT-D−treated patients in MADIT-CRT had a significant and meaningful reduction in LVESV, and these LVESV responders had reduced rates of cardiac events during long-term follow-up. **(Am J Cardiol 2014;113:1371−1377)**

Several randomized clinical trials have shown that cardiac resynchronization therapy (CRT) is associated with reduction in the risk of death and heart failure (HF) in patients with New York Heart Association (NYHA) class III or IV, reduced ejection fraction, and a wide QRS complex.[1,2] More recently, the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT),[3] the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE)[4] trial, and the Resynchronization-Defibrillation for Ambulatory Heart Failure[5] trial have demonstrated that the benefits of CRT also apply to patients with mild HF symptoms (NYHA class I or II), with particularly good results in patients with left bundle branch block (LBBB) and those with wider QRS complexes.[6−9] It is generally estimated that about 70% of patients treated with cardiac resynchronization benefit from this therapy.[10,11] However, this percent benefit has not yet been thoroughly investigated in patients with mild HF using a control group. The present study uses the implantable cardioverter-defibrillator (ICD)−only patients in the MADIT-CRT trial as a comparison group to define response versus nonresponse to CRT based on a prespecified reduction in left ventricular end-systolic volume (LVESV) between baseline and the 1-year follow-up echocardiogram. We hypothesized that the response to cardiac resynchronization therapy with a defibrillator (CRT-D) in patients without advanced HF is more favorable than the commonly stated 70% figure, especially in patients with LBBB, and that the greater the reduction in LVESV, the greater the subsequent clinical benefit from CRT.

[a]Heart Research Follow-up Program, University of Rochester Medical Center, Rochester, New York; [b]Department of Cardiology, Gentofte University Hospital, Copenhagen, Denmark; [c]Sheba Medical Center and Tel Aviv University, Tel Aviv, Israel; [d]Brigham and Women's Hospital, Boston, Massachusetts; and [e]University of California San Francisco Hospital, San Francisco, California. Manuscript received November 24, 2013; revised manuscript received and accepted January 14, 2014.

The MADIT-CRT study was supported by a research grant from Boston Scientific to the University of Rochester, with funds distributed to the coordination and data center, enrolling centers, core laboratories, committees, and boards under subcontracts from the University of Rochester (Boston Scientific, St. Paul, Minnesota).

The MADIT-CRT study is registered at *www.clinicaltrials.gov* (NCT00180271).

See page 1376 for disclosure information.

*Corresponding author: Tel: (585) 275-5391; fax: (585) 273-5283.

E-mail address: heartajm@heart.rochester.edu (A.J. Moss).

0002-9149/14/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2014.01.410

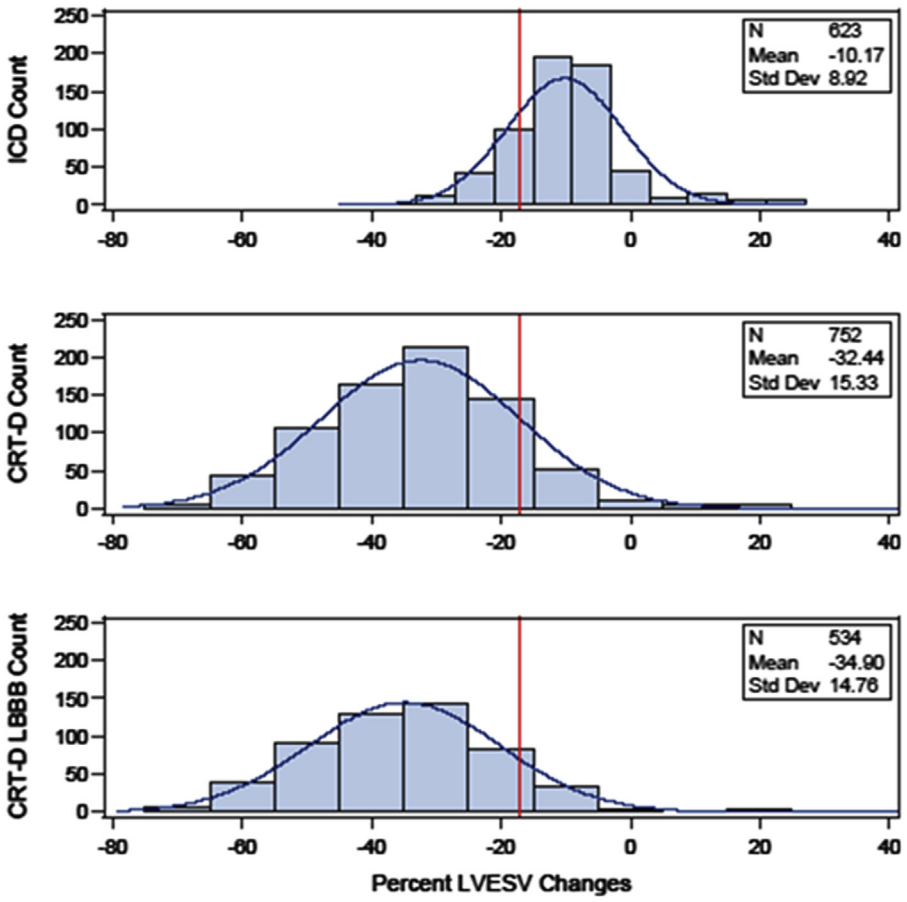

Figure 1. Histograms of the percent changes in LVESV between the baseline and 1-year echocardiogram in reference ICD-treated patients *(top)*, patients treated with CRT-D *(middle)*, and patients treated with CRT-D with LBBB *(bottom)*. The more negative percent change in LVESV, the greater the reduction in LVESV. The *vertical red line* indicates the top quintile of LVESV reduction in the reference ICD-treated patients corresponding to a value of −17% change or greater in LVESV. Eighty-eight percent of the patients treated with CRT-D and 91 percent of the patients treated with CRT-D with LBBB achieved a percent change (reduction) in LVESV more negative than −17%, and these patients are considered "responders" to CRT.

Methods

The MADIT-CRT trial included 1,820 patients with ischemic or nonischemic cardiomyopathy, QRS ≥130 ms, and left ventricular ejection fraction (LVEF) ≤30% who were in NYHA class I or II.[3] Patients were randomized to CRT-D or ICD implantation in a 3:2 ratio. The primary aim of the MADIT-CRT trial was to investigate whether the implantation of a CRT-D would reduce the risk of HF or death, whichever occurred first, compared with implantation of an ICD device. Patients were excluded from enrollment for a variety of previously reported reasons. The study enrolled patients from 110 hospital centers in Europe and North America. Previous publications have presented the design and primary results of the MADIT-CRT study.[3,12] The present study included 1,373 patients (75% of the total MADIT-CRT cohort) for whom paired baseline and 1-year echocardiographic measurements were available as previously published.[3]

From December 22, 2004 through June 24, 2009, a total of 1,820 patients were enrolled. After device implantation, patients were seen at scheduled visits at 1 month and then every 3 months afterward until the termination of the trial. Extended follow-up was conducted until September 10, 2010. The mean follow-up of the enrolled patients was 29.4 months.

Echocardiographic evaluations were performed according to study-specific protocol at baseline before device implantation (n = 1,809) and at 1-year follow-up. Paired echocardiograms from baseline and 1-year follow-up were available in 621 ICD-treated patients and 749 patients treated with CRT-D. The echocardiograms for this study were read at the echocardiographic core laboratory at Brigham and Women's Hospital[13] based on the protocols established by the American Society of Echocardiography.[14] The left ventricular and atrial volumes were measured by the Simpson method in the apical 4- and 2-chamber views and averaged, and the LVEFs were calculated according to standard methods. The coefficients of variation for end-diastolic volume, end-systolic volume, and LVEF were 5.2%, 6.2%, and 5.5%, respectively, as reported previously.[13]

To differentiate between LVESV responders and nonresponders, we prespecified CRT-D responders as the patients who at 1-year follow-up had a reduction in LVESV that corresponded to the top (best) quintile of LVESV reduction in the ICD-treated patients. The reduction was