Utility of 6-Minute Walk Test to Predict Response to Cardiac Resynchronization Therapy in Patients With Mild Heart Failure

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Clinical studies of heart failure (HF) generally utilize the 6-minute walk test (6MWT) for functional capacity (FC) assessment. However, data on the impact of cardiac resynchronization therapy (CRT) on 6MWT and its role to predict long-term outcomes in mild HF patients with CRT are lacking. We studied 1,381 subjects with mild HF enrolled in Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronization Therapy with 6MWT data at baseline and 1 year. We assessed the effects of CRT-D on percent change in 6MWT at 1 year by left bundle branch block (LBBB) status, identified independent predictors of 6MWT at 1 year, and evaluated the association between changes in 6MWT and risk for HF or death. Treatment with CRT-D versus implantable cardiac defibrillator (ICD) was not associated with a significant improvement in 6MWT at 1-year in LBBB subjects (2.2 % vs 0.0%, p = 0.428, but it was associated with a deterioration in 6MWT in non-LBBB subjects (4.1% vs 0.0%, p = 0.308). Multivariate analysis showed that each 5% reduction in 6MWT was independently associated with a corresponding 3% increase in the risk of subsequent HF or death (p = 0.014). In conclusion, our findings suggest that 6MWT has limited utility to identify CRT response in mild HF subjects with LBBB. However, 6MWT showed a signal toward deterioration in mild HF subjects with non-LBBB, and this was predictive of subsequent increased risk of HF or death. **(Am J Cardiol 2020;132:79−86)**

Cardiac resynchronization therapy (CRT) has been shown to improve clinical outcomes, left ventricular function, NYHA class, and quality of life.[1−7] Objective assessment of patient functional capacity (FC) in heart failure (HF) device trials commonly includes cardiorespiratory exercise testing to determine peak oxygen consumption or the 6-minute walk test (6MWT) developed by the American Thoracic Society,[8] that has been shown to predict mortality in HF subjects.[9−11] The 6MWT is a simple, reproducible, inexpensive test reflecting physical exertional levels associated with activities of daily living. Based on current recommendations, 6MWT is performed to evaluate change in response to interventions, with 54 m considered to be a clinically meaningful change.[8,12] While 6MWT test has been widely used for FC assessment in prior HF trials, data on the utility of changes in 6MWT to identify response to CRT, and to predict long-term outcomes in mild HF subjects are limited. Accordingly, in the present study we aimed to: evaluate the change in 6MWT from baseline to 1 year in ICD and CRT-D subjects enrolled in Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronization Therapy (MADIT-CRT), stratified by left bundle branch block (LBBB), and to assess the association between percent change in 6MWT and subsequent clinical outcomes in this population.

Methods

The design, protocol and results of MADIT-CRT have been published previously.[2,7,13] Briefly, 1,820 subjects with ischemic cardiomyopathy (New York Heart Association [NYHA] functional class I or II) or nonischemic cardiomyopathy (NHYA functional class II only), left ventricular ejection fraction (LVEF) of less than 30% and a prolonged QRS duration >130 ms were randomized to receive CRT-D or ICD therapy in a 3:2 ratio. All eligible subjects met the guideline criteria for ICD.[14] A total of 110 hospital centers from North America and Europe participated in this international multicenter trial. The study was in compliance with the Declaration of Helsinki and all enrolling sites had the protocol being approved by the local institutional review board. All subjects provided informed consent before enrollment.

The MADIT-CRT trial was carried out from December 22, 2004 through September 2010. After September 10, 2010, a long-term follow-up was conducted at 48 out of 88

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U.S. centers requested by the Food and Drug Administration for subjects enrolled in the United States (coordinated by the University of Rochester Medical Center, Rochester, New York), and at 23 of the 24 non-U.S. centers (coordinated by the Israeli Association for Cardiovascular Trials at Sheba Medical Center, Tel Hashomer, Israel).[7,15] The median follow-up of the enrolled subjects was 5.6 years. The present study population included all subjects for which a baseline and 1 year 6MWT was completed (n = 1,381).

Two-dimensional echocardiography was performed at baseline and at 1 year follow-up to assess changes in the left ventricular volumes including left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and LVEF in the study subgroups. Volumes were estimated by averaging those derived from the 2-chamber and 2-chamber views according to Simpson's method, and the ejection fraction was calculated according to the established American Society of Echocardiography protocols.[16] Echocardiography analysis was performed at the echocardiography core lab at Brigham and Women's Hospital, Boston, Massachusetts.

In this substudy of MADIT-CRT, we assessed both percent change in 6MWT between baseline and 1 year, and 6MWT at 1 year. Percent change in 6MWT was defined as the difference between baseline and 1 year values divided by the baseline values. Absolute change in 6MWT was categorized by the median change observed at 1 year. Therefore, all subjects above the median had improvement in 6MWT and those below the median had deterioration.

The primary outcome of the current study was long-term HF events or death, as assessed during the median follow-up of 5.6 years in MADIT-CRT. The diagnosis of HF was made by physicians un-blinded to treatment assignment, if subjects were exhibiting signs and symptoms consistent with congestive HF that resulted in intravenous decongestive treatment in an outpatient setting or augmented decongestive therapy with oral or parenteral medications during an in-hospital stay.

Commercially available transvenous devices (Boston Scientific) were used in the trial. Standard techniques were used to implant the CRT-D and ICD-only devices. Device testing and programming were performed as reported previously,[13] along with the provision of optimal pharmacologic therapy for HF in the 2 study groups. In the CRT-D group, the device was programmed to DDD with a lower rate of 40 bpm and hysteresis off. In the ICD-only group, the programmed pacing mode was VVI for single-chamber units and DDI for dual-chamber units, with lower rates of 40 bpm and hysteresis off in both single- and dual-chamber units.

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared in subjects by the median percent change in 6MWT, using Kruskal-Wallis test for continuous variables and χ^2 - test or Fisher's exact test for dichotomous variables, as appropriate.

Cumulative probabilities of HF or death events in the total population, as well as in the CRT-D and ICD subgroups were displayed by the median percent change in 6MWT at 1 year, according to the Kaplan-Meier method with comparisons of cumulative event rates by the log-rank test. Multivariable regression analysis was performed to identify predictors of the absolute value of 6MWT at 1 year, introducing treatment and LBBB interaction in the models.

Multivariable Cox proportional hazards regression analysis was used to evaluate the association between percent change in 6MWT at 1 year and the endpoint of long-term HF or death events. Multivariable Cox proportional hazards regression analysis models were adjusted for LBBB status, treatment and treatment interaction with LBBB, creatinine greater than 1.4 mg/dL at baseline, diabetes, ischemic status, LVESV index at baseline, prior HF hospitalization and QRS duration at baseline.

All statistical tests were 2-sided, a p value of <0.05 was considered statistically significant. Analyses were carried out with SAS software (version 9.4, SAS institute, Cary, NC).

Results

The present study included 1,381 subjects with available baseline and 1 year 6MWT data. The distribution of percent change in 6MWT among ICD and CRT-D subjects is presented in Figure 1. Notably, the median percent change was at the 0 point, therefore, all subjects above the median had improvement in 6MWT and those below the median had deterioration.

Baseline characteristics by median percent change in 6MWT are shown in Table 1. Subjects with improvement in 6MWT were significantly younger ($p = 0.008$) and had lower blood urea nitrogen (BUN; $p < 0.001$). There were no significant difference in baseline heart rate, gender, or etiology of cardiomyopathy in subjects by median 6MWT percent change.

When we assessed patient characteristics by 6MWT absence versus presence we found that patients with missing 6MWT at 1 year were older, more often Hispanic, they more frequently had ischemic cardiomyopathy, diabetes, hypertension, LBBB, they had more advanced HF status, and a higher creatinine and BUN, and they had a higher mortality rate (supplementary Table).

In CRT-D subjects with LBBB, percent change in 6MWT at 1-year was not significantly different in CRT-D versus ICD subjects (2.2 vs 0.0 %, $p = 0.428$). However, brain natriuretic peptide (BNP), echocardiographic parameters (LVESV, left ventricular end-diastolic volume, LV mass, and LVEF), and NYHA class were significantly improved in the CRT-D subjects compared with ICD subjects with LBBB (Figure 2). This signifies a disconnect between CRT-D associated improvement in echocardiographic and neurohormonal parameters in contrast to the 6MWT. However, CRT-D subjects with non-LBBB had a trend toward an increase in 6MWT at 1 year compared with ICD (CRT-D 4.1% vs ICD 0.0%, $p = 0.308$) despite significant improvement in echocardiography parameters and BNP (Figure 2).

We have compared changes in BNP levels in patients with and without deterioration in 6MWT at 12-month

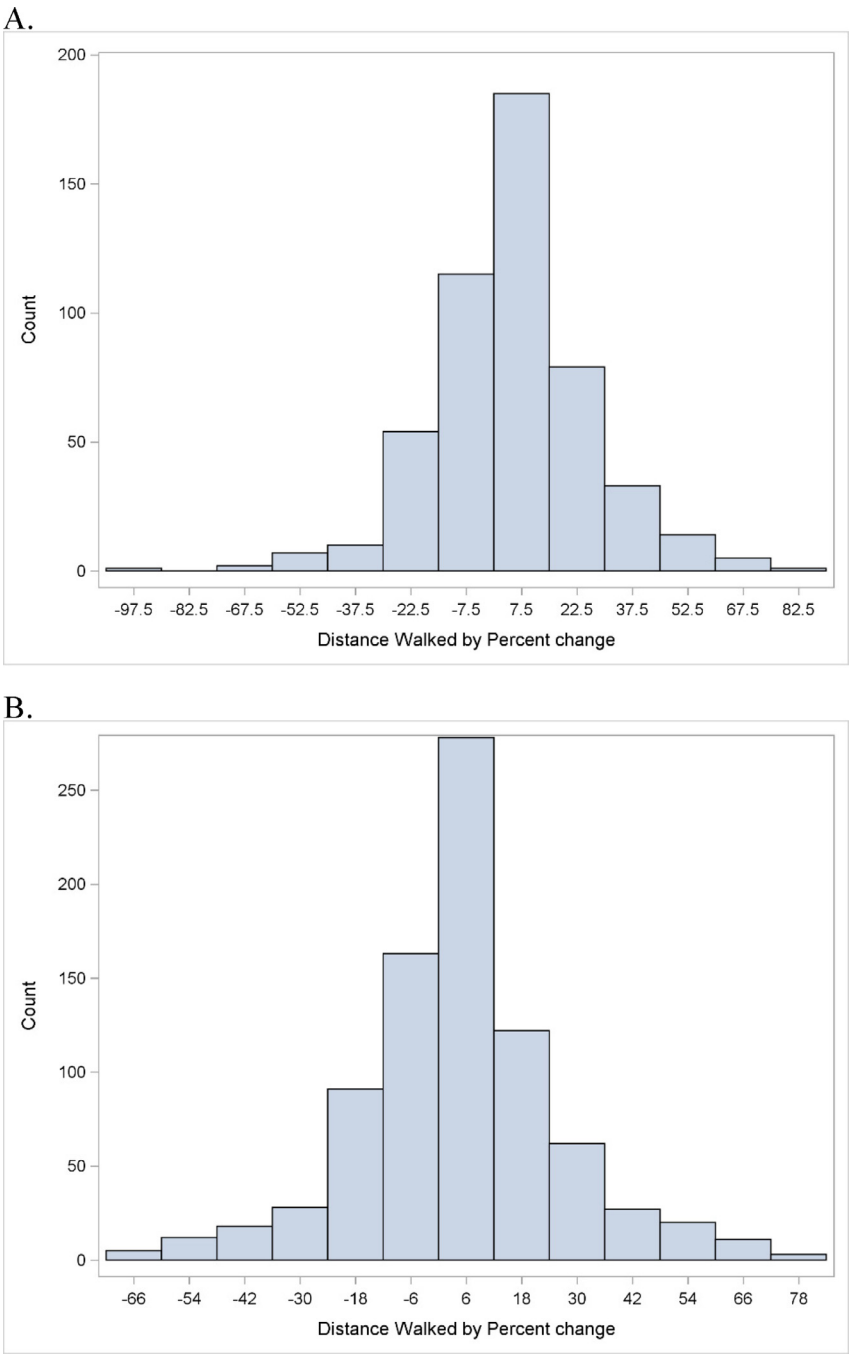

Figure 1. Distribution of 6MWT distance walked by percent change (A) in ICD subjects, (B) in CRT-D subjects.

and we found no significant differences (−17.38 vs −30.99, p = 0.231) suggesting that not only 6MWT is not a good marker characterizing CRT response but also deterioration in 6MWT is similarly not indicative of changes in BNP.

In the total population, subjects with greater than median percent change experienced a significantly lower rate of HF or death at 4 years of follow-up as compared with those who had a lower than median change (23% vs 29%, log-rank p value = 0.027; Figure 3). In ICD subjects, the percent change in 6MWT at 1 year was not associated with clinical outcomes (p = 0.509;Figure 3). However, subjects with CRT-D and a greater than median percent change in 6MWT experienced a significantly lower rate of HF or death at 4 years of follow-up (19 vs 28%, p=0.018;Figure 3).

Consistent with these findings, the percent change in 6MWT at 1 year was predictive of HF or death in multivariable models. Each 5 units percent change in 6MWT was associated with a 3% reduction in HF or death (p = 0.014). Similar findings were found in the ICD and CRT-D subgroups (Table 2).

Table 1
Clinical characteristics by percent change median in 6MWT at 1 year

Variable	Distance walkedpercent change		p value
	≤median(N = 690)	>median(N = 691)	
Baseline 6MWT (meters)	395.0 ± 96.5	349.5 ± 95.7	<0.001
Women	175 (25%)	162 (23%)	0.407
Randomized to CRT-D	430 (62%)	434 (63%)	0.851
Age at Enrollment (years)	64.7 ± 11.0	63.2 ± 10.8	0.007
Ischemic cardiomyopathy	372 (54%)	350 (51%)	0.225
Nonischemic cardiomyopathy	318 (46%)	341 (49%)	0.225
LVEF (%)	29 ± 3.4	28.7 ± 3.5	0.010
Left bundle branch block (LBBB)	502 (73%)	497 (72%)	0.731
Prior CHF Hospitalization	243 (36%)	257 (38%)	0.395
Diabetes Mellitus	202 (29%)	178 (26%)	0.143
Hypertension	428 (62%)	425 (62%)	0.814
Prior CABG	193 (28%)	188 (27%)	0.738
Prior PCI	178 (26%)	178 (26%)	0.975
Prior Myocardial infarction	285 (42%)	268 (40%)	0.359
Smoker	67 (10%)	89 (13%)	0.073
ACE Inhibitor or Angiotensin receptor blocker	660 (96%)	660 (96%)	0.900
Aldosterone	226 (33%)	210 (30%)	0.345
Amiodarone	49 (7%)	48 (7%)	0.910
Beta-blocker excluding Sotalol	639 (93%)	653 (95%)	0.152
Digitalis	167 (24%)	191 (28%)	0.145
Diuretic	446 (65%)	466 (67%)	0.272
Heart Rate (beats/min)	67.6 ± 10.8	67.4 ± 10.5	0.934
Body mass index (kg/m^2)	28.7 ± 5.2	28.3 ± 5.1	0.244
Blood urea nitrogen (mg/dl)	21.7 ± 9.1	20.3 ± 8.0	0.012
Creatinine (mg/dl)	1.17 ± 0.34	1.14 ± 0.30	0.206
Brain natriuretic peptide Level	124.9 ± 170.3	122.1 ± 154.9	0.250
Peak Systolic blood pressure (mm/hg)	121.9 ± 17.1	122.5 ± 17.0	0.573

Discussion

The present study provides several important implications for risk stratification and management of HF subjects scheduled for device therapy. We have shown that: (1) the change in 6MWT at 1 year following device implantation is not significantly different between ICD and CRT-D subjects in mild HF subjects with LBBB even though CRT-D was associated with significant improvement in echocardiographic and neurohormonal parameters; (2) in mild HF subjects with non-LBBB, CRT-D is associated with deterioration in 6MWT; (3) deterioration in 6MWT was predicted by older age, higher BMI, higher creatinine, prior myocardial infarction, and female gender; (4) percent change in 6MWT at 1-year predicted subsequent HF or death.

Six-minute walk test is commonly used in HF trials as a measure of functional capacity and as a predictor of response to therapy.[2,3,10,17–21] The MADIT-CRT trial showed that CRT-D is associated with a significant reduction in the risk of HF event or death in subjects with mild HF.[7] However, the present study does not show an improvement in 6MWT in CRT-D subjects despite significant improvement in echocardiographic parameters, biomarkers, and NYHA functional class in this population. Even in LBBB subjects most likely to respond to CRT, there was no significant improvement in 6MWT performance at 1 year. This could be explained by the fact that we enrolled a mildly symptomatic or asymptomatic HF population in MADIT-CRT, in whom, baseline functional capacity was relatively preserved at enrollment (~395 m). Likely, in HF subjects with mild or no symptoms, the 6MWT may not be sensitive enough to identify CRT response as denoted by echocardiographic and neurohormonal parameters, and raises new questions regarding the universal utility of 6MWT in HF clinical trials enrolling subjects with mild HF. Our findings are also in alignment with results of the previously published REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction (REVERSE) trial in mild HF subjects,[22] similarly showing non-significant change in 6MWT in the CRT-D arm.

Studies conducted in subjects with more advance HF however showed a significant improvement in 6MWT following implantation of a CRT device. The COMPANION study showed a 40 m average improvement in 6MWT at 6 months in subjects with CRT-pacemakers and a 46 m improvement in subjects with a CRT-defibrillator.[4] This is further highlighting the fact, that while the use of 6MWT is feasible for therapy effectiveness assessment in subjects with advanced HF, it is insufficient in those with mild HF.

Nevertheless, the 6MWT has been shown to predict survival in subjects with both mild and advanced chronic HF.[9,20,22] In a smaller study enrolling 188 consecutive subjects with moderate to severe HF, Castel et al showed that 6MWT distance was an independent predictor of mortality despite the beneficial effects of CRT.[23] Similarly, in our study, we show that changes in 6MWT by 1 year are predictive of subsequent HF or death. Utilizing information on

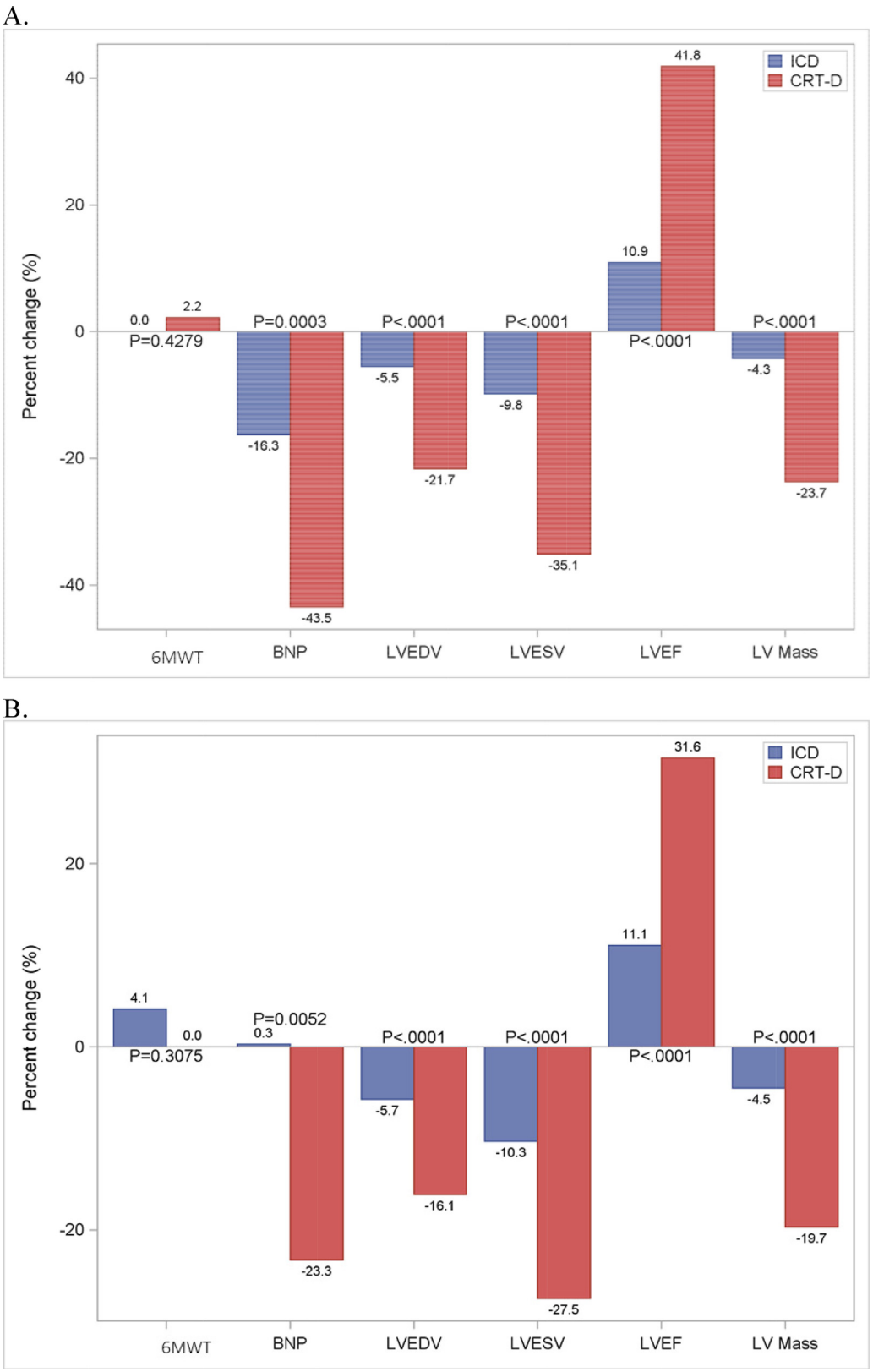

Figure 2. (A) Median percent change in 6MWT, echo parameters, BNP at 1 year in LBBB subjects. (B) Median percent change in 6MWT, echo parameters, BNP at 1 year in non-LBBB subjects.

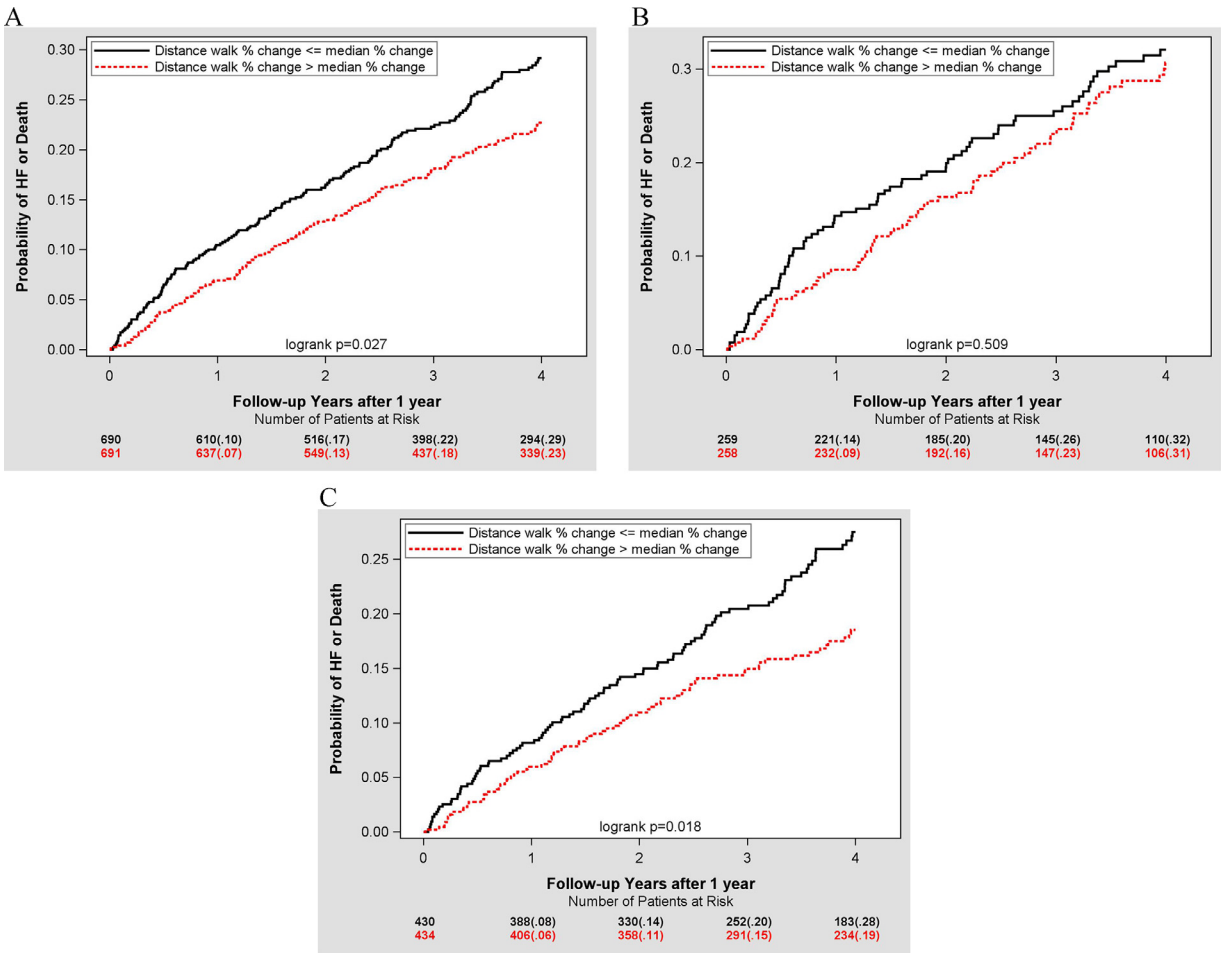

Figure 3. (A) Effect of 6MWT percent change at 1 year on clinical outcomes in total population. (B) Effect of 6MWT percent change at 1 year on clinical outcomes in ICD subjects. (C) Effect of 6MWT percent change at 1 year on clinical outcomes in CRT subjects.

changes in 6MWT could aid physicians in risk assessment of their HF subjects with devices.

On the other hand, there is increasing evidence in the literature suggesting that CRT-D implantation in non-LBBB subjects is not only ineffective but may be associated with potential harm.[24,25] Our present analysis of the 1 year 6MWT absolute distance walked in non-LBBB subjects revealed significant deterioration in 6MWT at 1 year further corroborating the potential harm in this subgroup. Whether this deterioration, CRT nonresponse, could be potentially ameliorated with intensification of medical treatment, or optimization of CRT device programming parameters (atrioventricular [AV]-delay optimization, VV-delay optimization) remains unclear.[26]

These results suggest that 6MWT, one of the most common tests of functional capacity in HF trials, does not predict CRT response in clinical trials enrolling mild HF subjects and it may have a limited utility as a tool for measuring clinical improvement. However, it may have potential utility in detecting harm, especially in non-LBBB subjects, with a greater sensitivity than deterioration in clinical endpoints such as HF or death. However, these findings need to be further tested and replicated in other cohorts with mild HF subjects and implanted devices.

Our study has multiple potential limitations. First, this is a post hoc analysis of a randomized clinical trial, and evaluating 6MWT was not part of the prespecified primary and secondary end points. Second, we had a number of subjects with missing 6MWT at either baseline or 1 year, potentially introducing bias. Missing data for 1 year 6MWT test results also includes mortality bias, patients who die in the first year will not have follow-up data. However, mortality rate was relatively low in MADIT-CRT due to the mild HF status of the patient population (3% annual mortality rate).[27] Third, this study enrolled mild HF subjects and therefore its results cannot be extrapolated to more advanced HF populations.

Table 2
Effects of 6MWT percent change at 12 months on heart failure or death

Heart failure/death	Hazard ratio	95% CI	p value
Total Population*	0.97	0.94−0.99	0.014
ICD†	0.96	0.92−1.01	0.099
CRT-D†	0.97	0.93−1.00	0.073

Multivariate analysis shows risk of subsequent HF or death for each 5% change in 6MWT.

* Models adjusted for LBBB status, treatment and treatment interaction with LBBB.

† All models are adjusted for creatinine greater than 1.4 mg/dL at baseline, diabetes, ischemic etiology, LVESV index at baseline, prior heart failure hospitalization and QRS.

In conclusion, the present substudy of MADIT-CRT showed no improvement in 6MWT at 1 year in CRT-D subjects with LBBB as compared with an ICD-only, despite significant CRT-D induced improvement in BNP and echocardiographic parameters. However, there was a signal of deterioration in non-LBBB subjects with CRT-D as compared to an ICD. The utility of 6MWT to assess CRT efficacy in mild HF subjects is limited.

Authors contribution

Spencer Z. Rosero, MD – Conceptualization, Methodology, Writing - Original draft preparation, Writing- Reviewing and Editing. Natalia Hernandez, MD – Writing - Original draft preparation, Writing - Reviewing and Editing. Ilan Goldenberg, MD – Supervision, Writing - Reviewing and Editing. Scott McNitt, MS – Formal analysis. Bronislava Plonsky MS – Formal analysis. Wojciech Zareba, MD, PhD – Writing - Reviewing and Editing, Supervision. Yonathan Buber, MD – Writing - Reviewing and Editing. Scott D. Solomon, MD – Writing - Reviewing and Editing. Valentina Kutyifa MD, PhD – Conceptualization, Methodology, Writing - Original draft preparation, Writing- Reviewing and Editing, Supervision.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.019.

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