

Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)

Sponsor's Executive Summary

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Introduction

Boston Scientific Corporation is the sponsor of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). To date, MADIT-CRT is the only randomized clinical trial to prospectively demonstrate the effectiveness of cardiac resynchronization therapy defibrillators (CRT-Ds) in the relative reduction of the risk of the combined endpoint of all-cause mortality or heart failure event, whichever occurs first, when compared to an implantable cardioverter defibrillator (ICD), in patients with early stages of congestive heart failure. Based on the trial design and the positive results of this trial, Boston Scientific is seeking an expanded indication for its CRT-Ds for the patient population studied.

Background

In patients with New York Heart Association (NYHA) Class III-IV heart failure, CRT-D has been shown in randomized, clinical trials as well as published results to reduce all-cause mortality, hospitalization, and symptoms, as well as improve exercise performance and quality of life. Food and Drug Administration (FDA) indications for CRT-D devices are currently restricted to this more advanced HF population.

Hypothesis

It was hypothesized that early intervention with CRT-D has the potential to slow the progression of heart failure in patients with asymptomatic or mild heart failure thus decreasing the incidence of death and/or heart failure events.

Study Results

MADIT-CRT was the first randomized clinical trial to prospectively meet its safety and effectiveness endpoints, demonstrating that Boston Scientific CRT-D systems slow the progression of heart failure in patients with low LVEF ($\leq 30\%$) and wide QRS (≥ 130 ms) who are NYHA Class II (ischemic or non-ischemic etiology) or NYHA Class I (ischemic etiology) while receiving optimal pharmacologic therapy. The CRT-D system-related complication-free rate observed was 85%, which was statistically significantly greater than the pre-specified boundary of 70%. Furthermore, the risk of all-cause mortality or heart failure event, whichever came first, was reduced by 34% with CRT-D when compared to ICD. The adjusted hazard ratio was 0.66, with 95% confidence interval (0.52 to 0.84), and $p < 0.001$. These successful MADIT-CRT results were reported in the New England Journal of Medicine (NEJM) on October 1, 2009.

Proposed Indications and Usage:

Based on the clinical data from the MADIT-CRT trial, Boston Scientific is seeking an expanded indication for its CRT-Ds for the patient populations studied.

The currently approved Indications and Usage statement is as follows:

Boston Scientific cardiac resynchronization defibrillators (CRT-Ds) are indicated for patients with moderate to severe heart failure (NYHA III/IV) who remain symptomatic despite stable, optimal heart failure drug therapy, and have left ventricular dysfunction ($EF \leq 35\%$) and QRS duration ≥ 120 ms.

Below is the proposed Indications and Usage statement to be supported by the submitted study results:

Boston Scientific Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with heart failure who receive optimal pharmacologic therapy for heart failure and who meet any one of the following classifications:

- *Moderate to severe heart failure (NYHA Class III-IV) with $EF \leq 35\%$ and QRS duration ≥ 120 ms (current indication)*
- *Mild heart failure (NYHA Class II) with $EF \leq 30\%$ and QRS duration ≥ 130 ms*
- *Asymptomatic heart failure (NYHA Class I) of ischemic origin with $EF \leq 30\%$ and QRS duration ≥ 130 ms*

Study Summary

An overview of the randomized patients, implant status, baseline characteristics and the primary safety and effectiveness results is below in Table 1.

Table 1: Overview of Patient Characteristics and Summary of Results

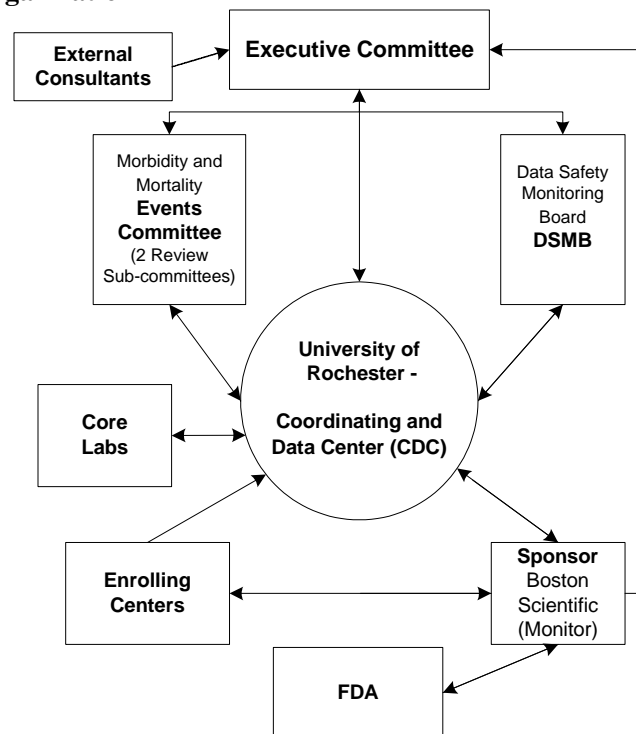
Data Item	Result
Number of enrolled patients	1820
Number of randomized patients (CRT-D/ICD)	1089 / 731
Number of implanted patients (CRT-D/ICD)	1078 / 712
Number of attempted patients (CRT-D/ICD)	1 / 0
Number of intent patients (CRT-D/ICD)	10 / 19
Mean follow-up time (\pm SD)	29.0 \pm 11.4 months
Implant phase	01/05/05 - 05/05/08
Number of centers	110
Patient Demographics	Result
Gender	75 % Male 25 % Female
NYHA Classification	15 % Class I Ischemic 40 % Class II Ischemic 45 % Class II Non-Ischemic
Mean Age (\pm SD)	64 \pm 11 years
Mean LVEF (\pm SD)	24 \pm 5 %
Mean QRS (\pm SD)	158 \pm 20 ms
Endpoint Summary	Result
Primary Safety	84.8% CRT-D System-Related Complication Free Rate 82.9% Lower One-Sided 95% Confidence Bound Safety Endpoint Passed (Lower Bound > 70%)
Primary Effectiveness	Adjusted Hazard Ratio (CRT-D/ICD) = 0.66 95% Confidence Interval = (0.52, 0.84) Effectiveness Endpoint Passed (p-value < 0.001)

Study Design

Study Organization

The MADIT-CRT Executive Committee was responsible for the clinical leadership and overall guidance of the study. The University of Rochester Coordinating Data Center (CDC) was responsible for overall study management, data management, data reporting and center communications. The Heart Failure Event Committee reviewed and adjudicated all potential heart failure events including all hospitalizations. The Mortality Endpoint Review Committee (MERC) reviewed and adjudicated all deaths. An independent Data Safety Monitoring Board (DSMB) met periodically to review the results of the study and to evaluate any safety or effectiveness issues that arose during the course of the study. There were also several core labs that reviewed data used to analyze tertiary endpoints. Boston Scientific (Guidant), as sponsor of the MADIT-CRT study, was responsible for all site monitoring, data compliance, and regulatory submissions/notifications. The pre-specified study organization detail is outlined below in Figure 1.

Figure 1: Study Organization



Methods

The MADIT-CRT trial was designed as a prospective, multi-center, randomized clinical study conducted in 110 centers in the United States (US), Europe, Canada, and Israel. Patients were

randomized in a 3:2 manner to receive either a commercially available Boston Scientific CRT-D or ICD, respectively. Randomization was stratified by clinical center and ischemic status. Each patient was analyzed in their respective randomized group (intention-to-treat), regardless of subsequent crossover or protocol adherence. MADIT CRT was an event driven trial that used a Wang-Tsiatis group-sequential design for interim analysis that allowed for early stopping for CRT-D benefit or harm. The study was designed to have a 95% power to detect a hazard ratio of 0.75.

The main entry criteria included:

- NYHA functional class II with non-ischemic or ischemic cardiomyopathy or NYHA functional class I with ischemic cardiomyopathy, AND
- Reduced left ventricular ejection fraction [$LVEF \leq 30\%$], AND
- Prolonged intraventricular conduction (QRS duration ≥ 130 ms), AND
- Optimal pharmacologic therapy (OPT) for heart failure.

Optimal Pharmacologic Therapy for Heart Failure

All subjects who participate in the study were required to receive optimal pharmacologic therapy for heart failure as defined below:

Beta Blockers: All subjects must have had a beta blocker prescribed to a therapeutic dose for the last 3 months, and have been stable for at least 1 month prior to enrollment, and if not, the reason that the physician did not prescribe a beta blocker must have been documented on a study case report form. The choice of selective or non-selective beta blocker use was left to the investigator's discretion.

Angiotensin Converting Enzyme (ACE) Inhibitors: All subjects must have had ACE inhibitor therapy prescribed to a therapeutic dose and have been stable for at least 1 month prior to enrollment, and if not, the reason that the physician did not prescribe ACE inhibitor therapy must have been documented on a study case report form.

Diuretics: All subjects must have had a diuretic prescribed, and if not, the reason that the physician did not prescribe diuretic therapy must have been documented on a study case report form.

In addition to the above agents, investigators were permitted to prescribe adjunctive medication per their medical discretion. These may have included, but were not limited to:

Angiotensin receptor blockers (ARBs)/Angiotensin II inhibitors: Angiotensin receptor blockers may have been prescribed in place of ACE inhibitors in those subjects who had previously failed or were contraindicated for ACE inhibitors.

Statins (lipid-lowering agents): All ischemic patients should have had a statin prescribed, and if not, the reason that the physician did not prescribe a statin must have been documented on a study case report form.

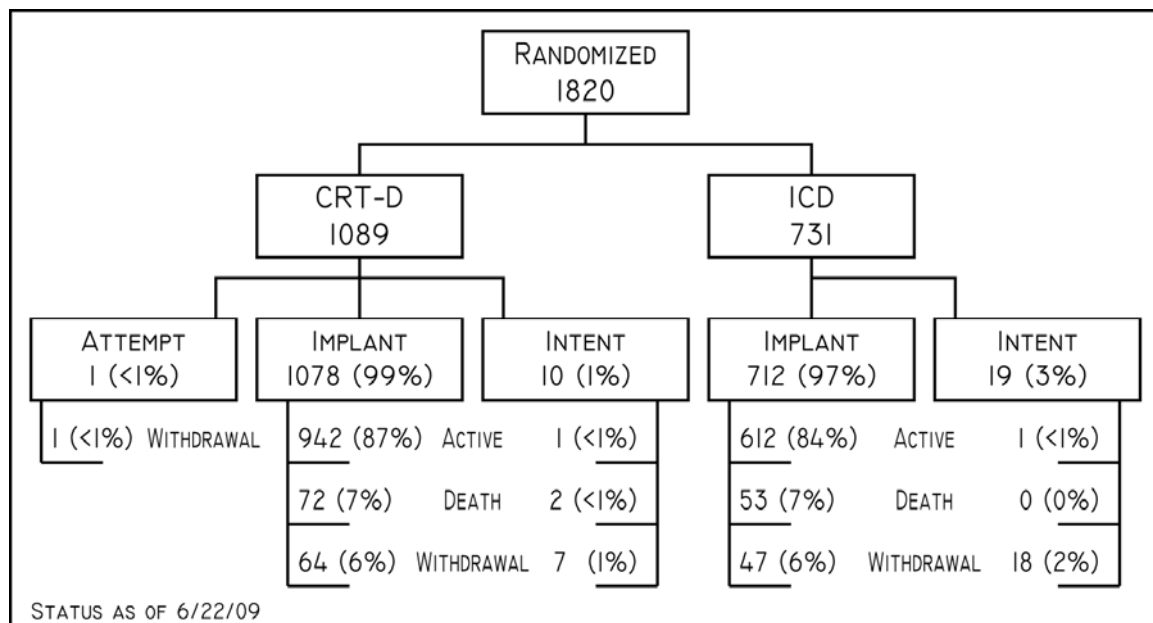
The use of antiarrhythmic medications was discouraged in this study. If the subject was receiving an antiarrhythmic medication, the medication had to have been identified on a study case report form. Digoxin, beta blockers (except Sotalol) and calcium channel blockers were not have been recorded as antiarrhythmic medications.

Patient Status

A total of 1820 patients were enrolled and randomized in the MADIT-CRT study; 1089 were randomized to CRT-D and 731 were randomized to ICD. The current patient status as of June 22, 2009 is outlined below in Figure 2.

Figure 2: Patient Status

All patients randomized, N= 1820



Patient Characteristics

The baseline patient characteristics of the 1820 randomized MADIT-CRT patients were well-balanced between the two therapy arms. While statistically significant differences were found between diastolic and systolic blood pressure, these differences are not considered clinically meaningful. The mean age of the patients was 64 ± 11 years, 75% of the patients were male, and 90% of the patients reported their race as white. A majority of the patients had ischemic heart disease (55%), 85% of the patients were classified as NYHA Class II, 71% of the patients had a left bundle branch block, and 62% of the patients had never been hospitalized for heart failure prior to enrollment. MADIT-CRT patients had a mean LVEF of $24 \pm 5\%$ and a mean QRS of 158 ± 20 ms. All patients were well-medicated on heart failure drugs: 96% of the patients were on an angiotensin converting enzyme (ACE) or angiotensin receptor blockers (ARB); 93% were on a beta blocker; 75% were on a diuretic; 32% were on an aldosterone antagonist; and 67% were on a statin.

The FDA posed a concern that the MADIT-CRT patients might not be as healthy as all-comer NYHA Class I/II patients with reduced LVEF. While that observation may be true for some studies; no evidence was found that this is applicable to MADIT-CRT. When compared to the demographic data available in the ICD registry, see Table 2 below, patients enrolled in the MADIT-CRT trial were younger and had lower levels of BNP. The proportion of patients with diabetes and renal status were remarkably similar between the ICD registry and the MADIT-CRT

population. Finally, the Kansas City Cardiomyopathy Questionnaire's (KCCQ) Overall Summary Scores also support the conclusion that MADIT-CRT patients were not less healthy than the population from which patients were recruited. (QOL data is provided in the response to FDA's question SK1 in Tab 6.2 of this panel pack.)

Table 2: Comparison of MADIT-CRT Baseline Characteristics to ICD Registry

Characteristic	Class I		Class II – Ischemic		Class II - Non-ischemic	
	Registry (n=1511)	MADIT- CRT (n=265)	Registry (n=6857)	MADIT CRT (n=734)	Registry (n=3381)	MADIT CRT (n=821)
Age (years)	71	68	72	67	66	61
Male sex (%)	87	91	84	86	63	60
BUN (mg/dL)	21	22	22	23	20	21
BNP (pg/mL)	367	143	526	134	429	112
Diabetes (%)	34	27	38	38	28	25

The data supports the conclusion that MADIT-CRT patients were either similar to, or somewhat healthier, in some respects than the general ICD population for which labeling is ultimately intended.

Baseline 6 Minute Walk Test

FDA posed a concern that the baseline 6-minute walk distance test (6MWT) observed in the MADIT-CRT trial was indicative of a more advanced heart failure population than NYHA Class I/II. To assess how the MADIT-CRT population compares with respect to baseline 6MWT, a comparison to normals, other NYHA Class I/II populations receiving CRT, and other NYHA Class III/IV populations receiving CRT, as well as HF-ACTION was performed.

Regression equations based on age, sex, and body mass index were derived from healthy adults¹. For reference purposes, a mean range and lower limit of normal (LLN) were calculated separately for males and females assuming a mean age of 65 years and then weighted in a proportion of 75%

¹ Enright and Sherrill Am J Respir Crit Care Med 1998;158:1384-7

male/25% female since that proportion corresponds to most CRT studies. The LLN for this range is plotted in Figure 3.

Analysis of three randomized studies of CRT versus No CRT including NYHA Class I/II populations have been performed: MIRACLE ICD II², CONTAK CD³; and REVERSE⁴. The baseline results are illustrated in Figure 3. These values are consistent not only with each other, but with the lower limit of what would be expected in normal, healthy adults.

A more appropriate comparison for the average 6MWT baseline in a sicker population including NYHA Class III/IV would be the CONTAK CD³, MIRACLE⁵, MIRACLE ICD⁶, RHYTHM ICD⁷, and COMPANION⁸ studies, which all randomized CRT versus No CRT. The average 6MWT distance in these studies was ~ 90m less than that seen in the MADIT-CRT study. Compared to the Class I/II population, the baseline 6MWT distances in Class III/IV patients were substantially diminished with respect to the lower limit of normal and therefore afforded considerable space for improvement. PROSPECT was a prospective registry of NYHA Class III/IV CRT patients with a baseline 6MWT comparable to the randomized studies.

² Abraham *et al* Circulation 2004;110:2864-8

³ Higgins *et al* JACC 2003;42(8):1454-9. Baseline data from CONTAK CD PMA Clinical Report, June 2001.

⁴ Linde *et al* JACC 2008;52:1834-43

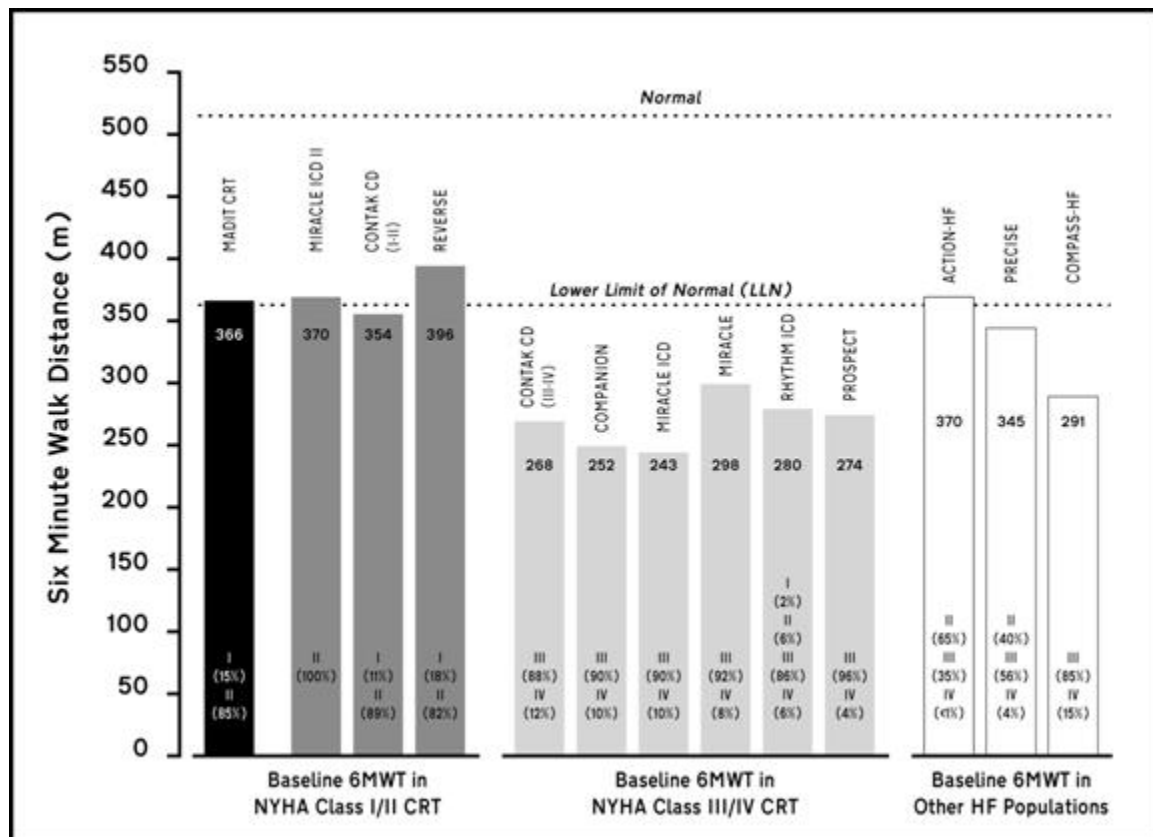
⁵ Abraham *et al* N Engl J Med 2002;346:1845-53

⁶ Young *et al* JAMA 2003; 289 (20): 2685-2694

⁷ Epic/Atlas Summary of Safety and Effectiveness, P030054, June 30, 2004

⁸ Bristow *et al* N Engl J Med 2004;350-2140-50

Figure 3: Comparative Analysis of Baseline Six Minute Walk Tests in Heart Failure Trials



Six minute walk tests have been performed in other heart failure populations. HF-ACTION was designed to determine if exercise training could improve outcomes in heart failure patients⁹. Of the patients in the HF-ACTION trial over 60% were class II, and only ~1% were class IV. Furthermore, 45% of HF-ACTION patients already had an ICD or CRT implanted at the time of enrollment. Given the nature of the HF ACTION trial was to study the effects of an exercise program on HF status there may have been some enrollment bias towards healthier patients willing to undertake the requirements of the study. It is therefore not surprising that the baseline 6MW values were not dramatically different to those in the MADIT-CRT study.

Similar to HF-ACTION, the PRECISE trial of the beta blocker carvedilol emphasized six minute walk testing as part of its investigational plan and recruited patients based on their ability to walk¹⁰. It also had a relatively high baseline 6MWT, suggesting that higher values might be attained if entry criteria are based on exercise performance. In contrast, the COMPASS-HF study

⁹ O'Connor *et al* JAMA 2009; 301 (14): 1439-1450

¹⁰ Packer *et al* Circulation 1996;

recruited NYHA Class III/IV heart failure patients with no emphasis on ability to perform a six minute walk test¹¹. These patients had a baseline 6MWT distance more similar to that of the NYHA Class III/IV CRT patient population.

Based on comparison of baseline 6MWT distance and other baseline characteristics, the MADIT CRT patients are similar to, if not healthier, than typical NYHA I/II patients with low ejection fractions. Therefore the results from the MADIT CRT study should be consistent with what will be seen in general practice

Primary Objectives

Safety Objective

The safety objective was to determine if the CRT-D system-related complication-free rate observed was greater than 70% after three months post implant.

The safety endpoint defined the system as including all components required for implantation of the CRT-D device, leads, and the associated implant procedure. A complication was defined as a clinical event that resulted in invasive intervention after implant, injury, or death, including at least one of the following outcomes:

- Life-threatening condition
- Significant, persistent, or permanent disability
- Invasive intervention as a corrective action to preclude permanent impairment/damage (e.g., device explant, lead revision, ventilation)
- Congenital anomaly
- Hospitalization or prolongation of an existing hospitalization
- Permanent loss of device function

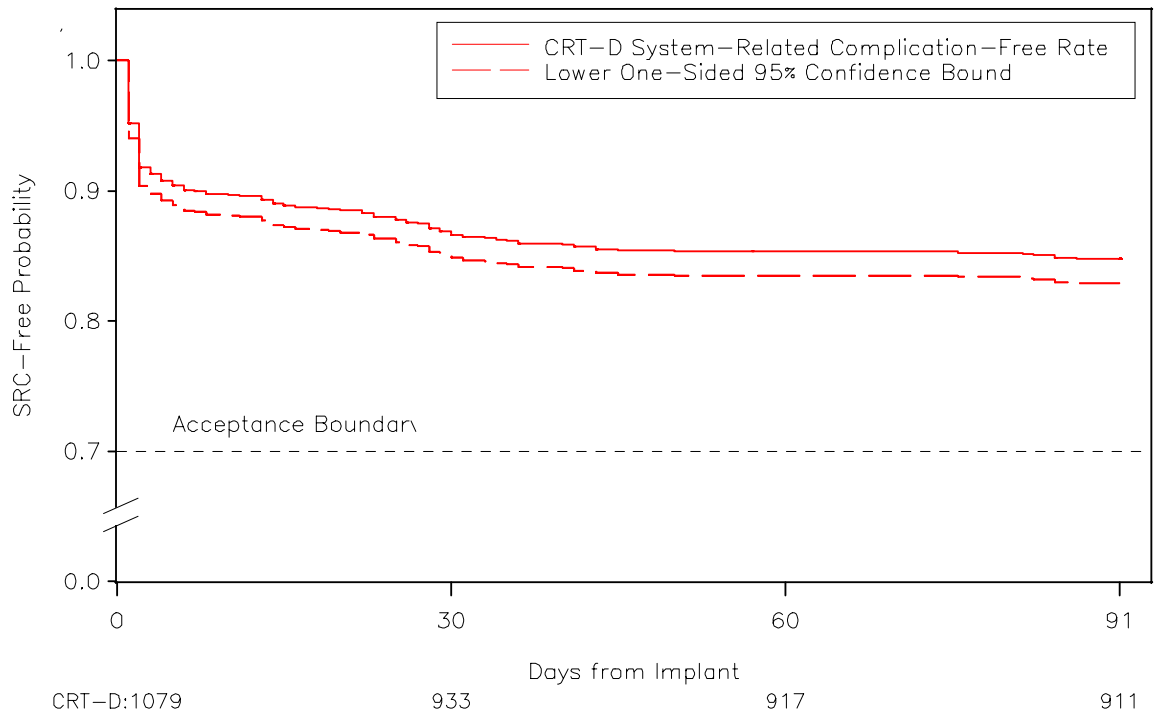
Safety Results:

A total of 1079 patients underwent an implant procedure and were included in the safety endpoint. Of these, 164 unique patients experienced 214 system-related complications (SRC)s within 91 days post-implant. The CRT-D Kaplan-Meier system-related complication-free rate was 84.8% with a lower one-sided 95% confidence bound of 82.9%. This rate was statistically

¹¹ Bourge RC *et al* JACC 2008;51:1073-9. Baseline six minute walk data downloaded from http://www.fda.gov/OHRMS/DOCKETS/AC/07/briefing/2007-4284b1_04.pdf

significantly greater than 70% and therefore passed the pre-specified safety endpoint. The Kaplan-Meier system-related complication-free graph is shown in Figure 4.

Figure 4: CRT-D Kaplan-Meier Curve of Time to System-Related Complication



Of the 214 system-related complications that occurred, the cause of the event was related to the implant procedure in 84 events (39.3%), the LV lead in 62 events (29.0%), the RA lead in 35 events (16.4%), and the remaining 15.3% of events were related to the PG or RV lead. A summary of the CRT-D system-related complications that contribute to the safety endpoint is shown below in Table 3. The sum of patients across categories does not equal the total number of unique patients because some patients had more than one SRC.

Table 3: CRT-D System-Related Complications

Complication	Number of Events	Number of Patients	Complication Free Rate (%)	Lower One-Sided 95% Confidence Bound (%)
Procedure	84	75	93.0	91.6
AV block	6	6	99.4	98.9
Adverse reaction	6	6	99.4	98.9
Hematoma - Pocket (<=30 days post-implant)	14	14	98.7	98.0
Inadvertent VT/VF	4	4	99.6	99.2
Other - Lead - Procedure	5	5	99.5	99.0
Pericardial effusion	4	3	99.7	99.3
Pneumothorax - Procedure	15	15	98.6	97.9
Post-surgical infection (<= 30 days post-implant)	5	5	99.5	99.0
Renal failure due to contrast media - Procedure	4	4	99.6	99.2
Thromboembolic events	8	8	99.3	98.7
Other Procedure *	13	13	98.8	98.1
LV Lead	62	57	94.7	93.5
Dislodgment	51	46	95.7	94.6
Extracardiac stimulation - LV	9	9	99.2	98.6
Other LV Lead **	2	2	99.8	99.4
PG **	16	16	98.5	97.8
RA Lead	35	35	96.7	95.7
Dislodgment	33	33	96.9	95.9
Other RA Lead **	2	2	99.8	99.4
RV Lead	15	15	98.6	97.9
Dislodgment	8	8	99.3	98.7

Complication	Number of Events	Number of Patients	Complication Free Rate (%)	Lower One-Sided 95% Confidence Bound (%)
Elevated threshold - RV	5	5	99.5	99.0
Other RV Lead **	2	2	99.8	99.4
Other ***	2	2	99.8	99.4
Total System-Related Complications	214	164	84.8	82.9

* Procedure related events that occurred three times or fewer: Arterial perforation - Procedure (1), Coronary venous perforation without tamponade (2), Inadvertent SVT (1), Myocardial perforation with tamponade (3), Other - PG system - Procedure (1), Pleural effusion - Procedure (1), Post-surgical pocket hemorrhage (2), Seroma - Pocket (<=30 days post-implant) (1), Venous occlusion (1).

** Device related events that occurred three times or fewer: Elevated threshold - LV (1), Insulation breach - LV (1), Early ERI - Random component failure (2), Elevated DFT - Defibrillation (3), Elevated threshold - RV (1), Extracardiac stimulation - LV (2), Inappropriate tachy therapy - Noise (1), Inappropriate tachy therapy - SVT (1), Infection (> 30 days post-implant) (3), Migration (1), Programmer / Software error code (1), Unable to convert - Defibrillation (1), Unable to capture - RA (2), Elevated DFT - Defibrillation lead (1), Unable to convert - Defibrillation lead (1).

*** Other events that occurred three times or fewer: Pulmonary edema - Heart failure (1), Systemic infection (1).

The system-related complications contributing to the safety endpoint that occurred most frequently (incidence greater than 1.0%) are described in greater detail below.

The most frequent system-related complications related to the procedure were:

- Pneumothorax [15 events in 15 patients (1.4%)]: Nine events were corrected with an invasive intervention and six required no intervention other than a prolonged hospitalization.
- Hematoma [14 events in 14 patients (1.3%)]: Twelve events were corrected with an invasive intervention and two required a pressure dressing and a prolonged hospitalization.

The most frequent system-related complications related to the device were:

- LV lead dislodgment [51 events in 46 patients (4.3%)]: Forty one patients had a single event requiring invasive intervention and five patients had a second dislodgment requiring an additional intervention. Successful restoration of CRT-D was accomplished

- in 41/46 (89%) patients who either received a new lead or had the existing lead revised. The remaining five patients (11%) had the lead removed and the LV lead port plugged.
- RA lead dislodgment [33 events in 33 patients (3.1%)]: All 33 RA dislodgments were successfully corrected with an invasive intervention.

None of the PG-related complications occurred at a frequency greater than 1.0%.

Safety Endpoint Conclusion

The CRT-D system-related complication-free rate observed within 91 days post-implant was 84.8%, with a lower one-sided 95% confidence bound of 82.9%. This result was statistically significantly greater than the pre-specified boundary of 70%. The safety endpoint was met; thus, Boston Scientific CRT-D systems have demonstrated safety in the MADIT-CRT patient population.

Primary Effectiveness Objective

The primary effectiveness objective was to determine whether CRT-D resulted in a significant reduction in the combined endpoint of all-cause mortality or heart failure event, whichever came first, when compared to ICD.

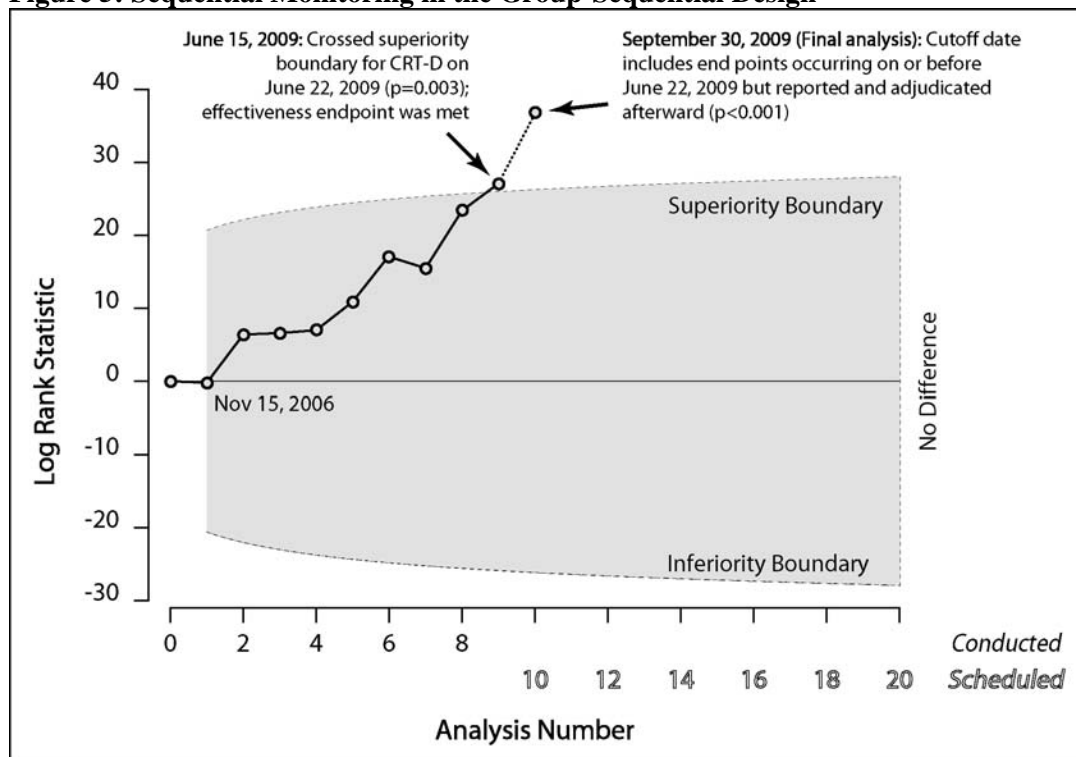
Heart failure events were documented by clinical data reports from the hospital or out-patient record and were reviewed, classified, and adjudicated by the Heart Failure Event Committee. A *Heart Failure Event* was defined as a patient having symptoms and/or signs consistent with congestive heart failure in an in-patient or out-patient setting and receiving either:

- Intravenous decongestive therapy (IV diuretics, IV nesiritide, IV inotropes), that did not involve formal in-patient hospital admission, regardless of the setting (i.e. in an emergency room setting, in the physician's office, etc.) (out-patient), or
- An augmented heart failure regimen with oral or intravenous medications during an in-hospital stay (formal hospital admission is defined as admission to hospital that includes a calendar date change) (in-patient).

Primary Effectiveness Results

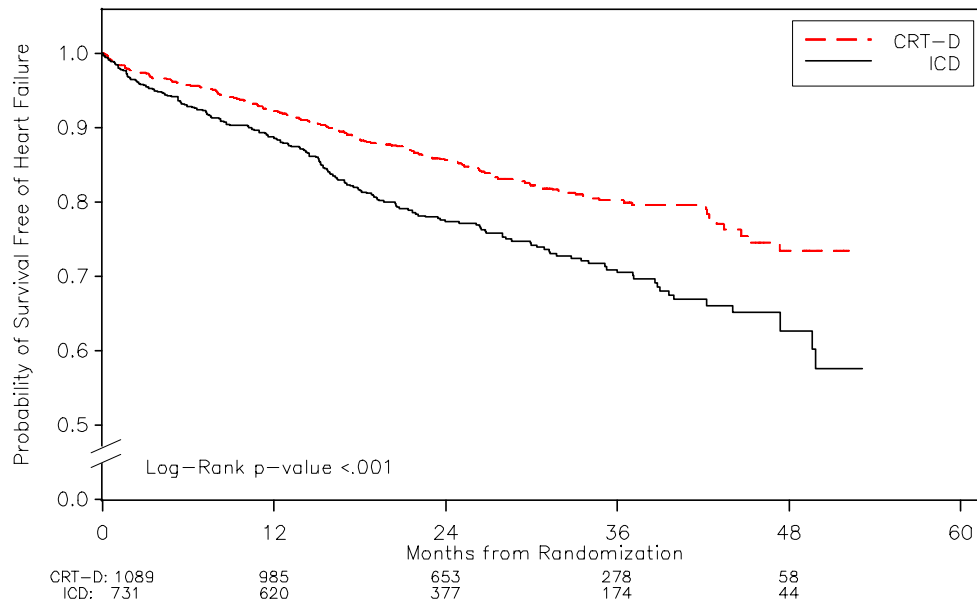
Figure 5 below demonstrates the sequential monitoring performed by the DSMB over the course of the study. On June 22, 2009, the ninth scheduled interim analysis indicated that the primary effectiveness endpoint was met ($p = 0.003$).

Figure 5: Sequential Monitoring in the Group-Sequential Design



CRT-D was associated with a statistically significant reduction in the combined endpoint of all-cause mortality or heart failure event, whichever occurred first, when compared to ICD (adjusted log-rank $p<0.001$). The Kaplan-Meier curves demonstrate separation in the early months and continue to separate throughout the subsequent follow-up period as shown below in Figure 6. The adjusted hazard ratio was 0.66, with 95% confidence interval (0.52 to 0.84), and $p<0.001$.

Figure 6: Kaplan-Meier Curves of Time to All-Cause Mortality or HF Event



The components of the primary effectiveness endpoint are shown below in Figure 7 and Table 4. The hazard ratio for all-cause mortality or heart failure event was not adjusted for the sequential design of the trial; therefore it differs from the adjusted hazard ratio of 0.66. A higher percentage of patients had a primary event in the ICD group as compared to the CRT-D group. The primary endpoint was predominantly driven by a reduction in heart failure events with CRT-D. Most heart failure events occurred in the in-patient setting.

Figure 7: Primary and Secondary Effectiveness Endpoint Components

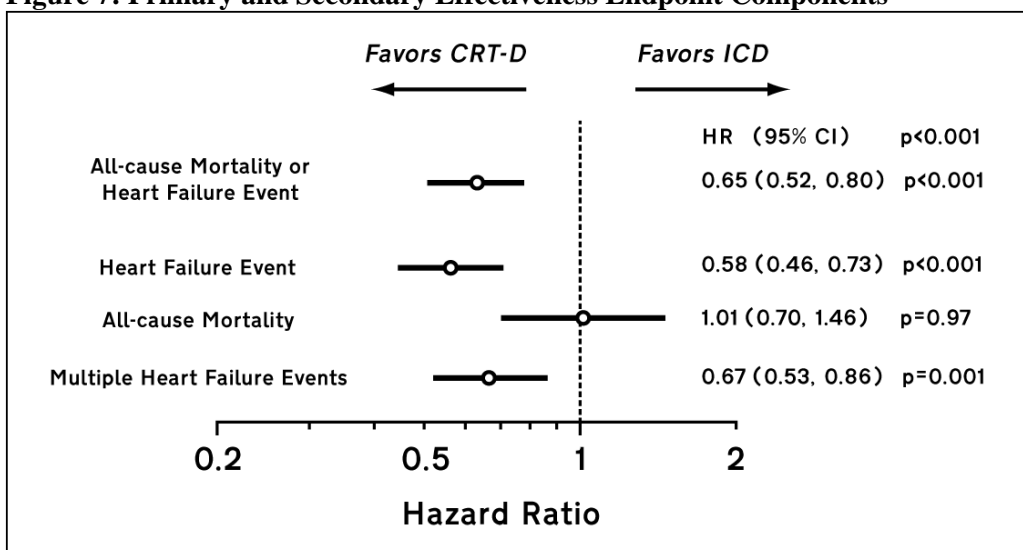


Table 4: Primary Effectiveness Endpoint Components

Item	Number of Patients (% of All Patients in Treatment Group)			
	ICD (N=731)	CRT-D (N=1089)	Hazard Ratio (95% Confidence Interval)	P-value
Patients with Primary Endpoint Event	188 (26%)	188 (17%)	0.65 (0.52, 0.80)	<.001
Patients with All-Cause Mortality at Any Time*	53 (7%)	74 (7%)	1.01 (0.70, 1.46)	0.970
Patients with HF Event	170 (23%)	152 (14%)	0.58 (0.46, 0.73)	<.001
Inpatient HF Event	142 (19%)	137 (13%)		
Outpatient HF Event	28 (4%)	15 (1%)		

* This category includes all deaths, including those that occurred after the first heart-failure event.

Primary Effectiveness Conclusion

In the MADIT-CRT study, CRT-D was associated with a statistically significant reduction by 34% in the relative risk of death or heart failure event as compared to ICD. The primary effectiveness endpoint was met; thus, Boston Scientific CRT-D systems slow the progression of heart failure by reducing the risk of all-cause mortality or heart failure event in the MADIT-CRT patient population.

Secondary Objective

The secondary objective was to evaluate the effects of CRT-D, relative to ICD, on the patient-specific rates of multiple heart failure events over the full study period.

Secondary Effectiveness Results

A summary of the number of all heart failure events experienced for all patients according to treatment group is presented below in Table 5. The number of CRT-D patients without a HF event was 86.0% compared to those with an ICD (76.7%).

Table 5: Number of Heart Failure Events by Treatment Arm

Number of HF Events	Number of Patients (% of All Patients in Treatment Group)	
	ICD (N=731)	CRT-D (N=1089)
0	561 (76.7%)	937 (86.0%)
1	103 (14.1%)	94 (8.6%)
2 +	67 (9.2%)	58 (5.3%)

Rates of heart failure events are presented two ways in Table 6 below, separately for each treatment group: first as the count of heart failure events per 100 patients and second as the count of heart failure events per 100 patient-years of follow-up. Patients randomized to ICD experienced 44 HF events for every 100 patients and 18.6 HF events for every 100 patient-years of follow-up, whereas patients randomized to CRT-D experienced 25 HF events for every 100 patients and 10.1 HF events for every 100 patient-years of follow-up.

Table 6: Rate of All Heart Failure Events by Treatment Group

Randomized Arm	Total HF Events	Total Follow-up (Years)	Total HF Events per 100 Patients	Total HF Events per 100 Patient-Years
ICD	324	1743.2	44	18.6
CRT-D	269	2656.8	25	10.1

The risk of experiencing a heart failure event was almost nine times greater if a previous event had occurred. A CRT-D benefit was still observed after accounting for this dependency of events. CRT-D was associated with a statistically significant reduction in the number of multiple heart failure events, as evidenced by a hazard ratio of 0.67 (95% confidence interval of 0.53 to 0.86, and $p=0.001$) and is presented in Table 7. This corresponds with a 33% overall reduction in the risk of multiple heart failure events, comparing CRT-D to ICD.

Table 7: Andersen-Gill Multiple HF Events Model

Covariate	Hazard Ratio		
	Estimate	95% Confidence Interval	P-value
Treatment (CRT-D/ICD)	0.67	(0.53, 0.86)	0.001
Previously experienced HF event in study	8.84	(6.84, 11.43)	<.001

Secondary Effectiveness Conclusion

In the MADIT CRT study, CRT-D was associated with a statistically significant reduction in the risk of multiple heart failure events by 33% when compared to ICD, meeting the secondary endpoint. Thus, Boston Scientific CRT-D systems were effective in slowing the progression of heart failure by reducing the occurrence of multiple heart failure events in the MADIT-CRT patient population over the course of the study.

Tertiary Objectives

For a complete listing of the tertiary endpoints and results, refer to the Clinical Report, which is also provided in the panel packet.

Tertiary Objective -- All-Cause Mortality

One of the tertiary objectives was to evaluate the effects of CRT-D on all-cause mortality.

All-Cause Mortality Results:

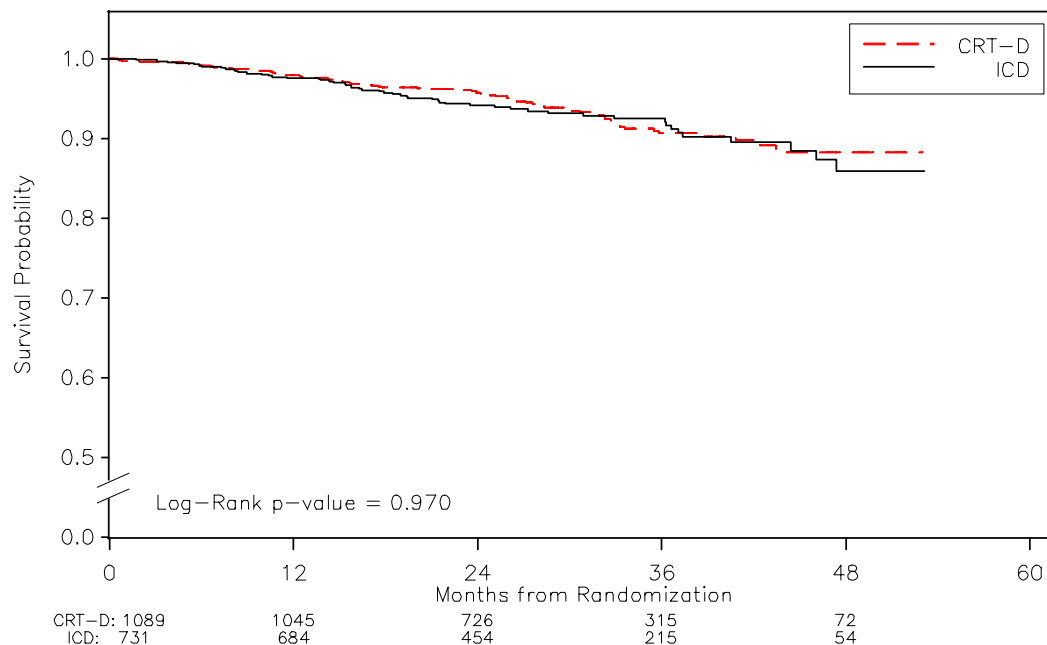
Death occurred in 6.8% (n=74) of the patients in the CRT-D group and 7.3% (n=53) of the patients in the ICD group. The hazard ratio for all-cause mortality was 1.01, with a 95% confidence interval (0.70 to 1.46), and p=0.97 and is shown below in Table 8. These results indicated a similar all-cause mortality rate between the treatment groups.

Table 8: All-Cause Mortality

Outcome	Hazard Ratio	95% Confidence Interval	P-value
All-cause Mortality	1.01	(0.70, 1.46)	0.970

The log-rank test confirmed there was no difference (p=0.97) between the treatment groups in the survival distribution as shown below in Figure 8.

Figure 8: Kaplan-Meier Curves of Time to All-Cause Mortality



All-Cause Mortality Conclusion

There was no evidence of a difference in mortality between the treatment groups.

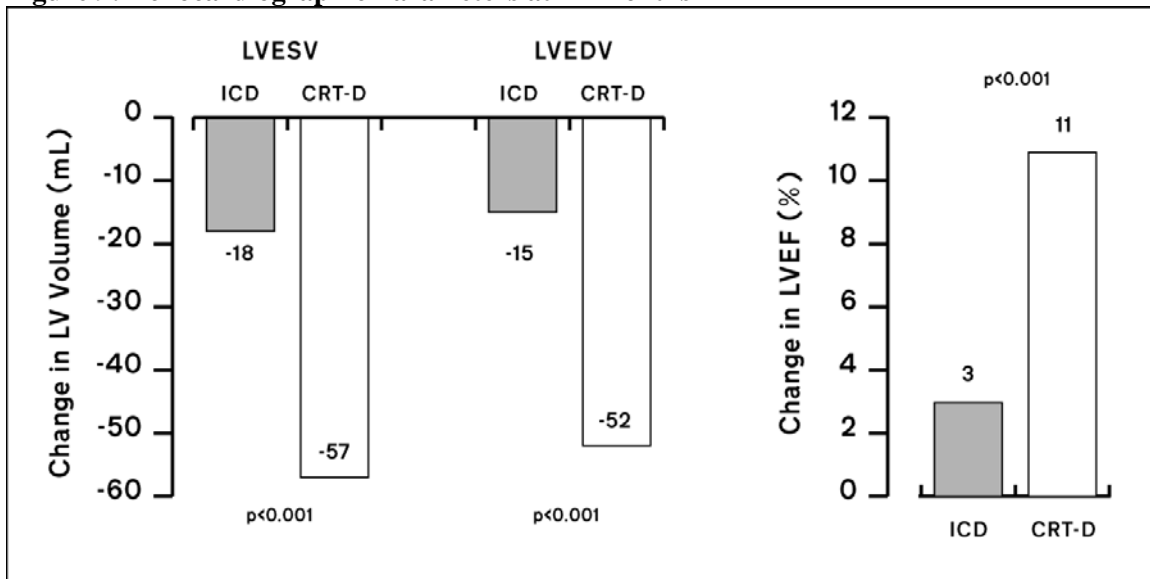
Tertiary Objective – Echocardiographic Structure and Function:

A tertiary objective was to evaluate the effects of CRT-D, relative to ICD, on the changes from baseline to one year in echo-determined left ventricular internal volume at end-systole (LVESV) and at end-diastole (LVEDV). The changes from baseline to one year in left ventricular ejection fraction (LVEF) were also evaluated,

Echocardiographic Structure and Function Results

The echocardiographic volumes and ejection fraction at baseline and at 12 months are presented below in Figure 9. At 12 months, the mean change in LVESV in the CRT-D group was a reduction of 57 ml, as compared to 18 ml in the ICD group ($p < 0.001$). Similarly, the mean change in LVEDV at 12 months in the CRT-D group was a reduction of 52 ml, as compared to 15 ml in the ICD group ($p < 0.001$). Additionally, the mean change at 12 months in LVEF in the CRT-D group was an improvement of 11%, as compared to 3% in the ICD group ($p < 0.001$).

Figure 9: Echocardiographic Parameters at 12 Months



Echocardiographic Structure and Function Conclusion

CRT-D was associated with a statistically significant reduction in left ventricular volumes and a statistically significant improvement in left ventricular ejection fraction as compared to ICD. Thus, in the MADIT-CRT study, CRT-D improved cardiac structure and function. These results further support the conclusion that CRT-D slows the progression of heart failure in the MADIT-CRT patient population.

Study Conclusion

In the MADIT-CRT study, the safety and primary effectiveness endpoints were met. The CRT-D system-related complication-free rate between implant and three months of follow-up was 85%; this result was statistically significantly greater than the pre-specified boundary of 70%. CRT-D also reduced the relative risk of the combined endpoint of all-cause mortality or heart failure event by 34% as compared to ICD ($p < 0.001$). Thus, the MADIT-CRT data demonstrate the safety and effectiveness of Boston Scientific CRT-D devices in slowing the progression of heart failure in NYHA Class I ischemic and NYHA Class II ischemic and nonischemic patients with low ejection fraction and wide QRS duration. Patients in the CRT-D group showed a statistically significant reduction in left ventricular volumes and statistically significant improvement in left ventricular ejection fraction than patients in the ICD group, further supporting the conclusion that CRT-D slows the progression of heart failure in the MADIT-CRT patient population.

Subgroup Analyses

MADIT-CRT was not powered or designed to demonstrate significance in subgroups. Such analyses are usually considered to be hypothesis-generating and caution should be exercised when interpreting subgroup results to avoid potentially misleading conclusions regarding the data. However, effects attributed to a particular subgroup may nonetheless exist and subgroup analysis can reveal important information about the therapy. For validity of the subgroup analyses, the following was considered:

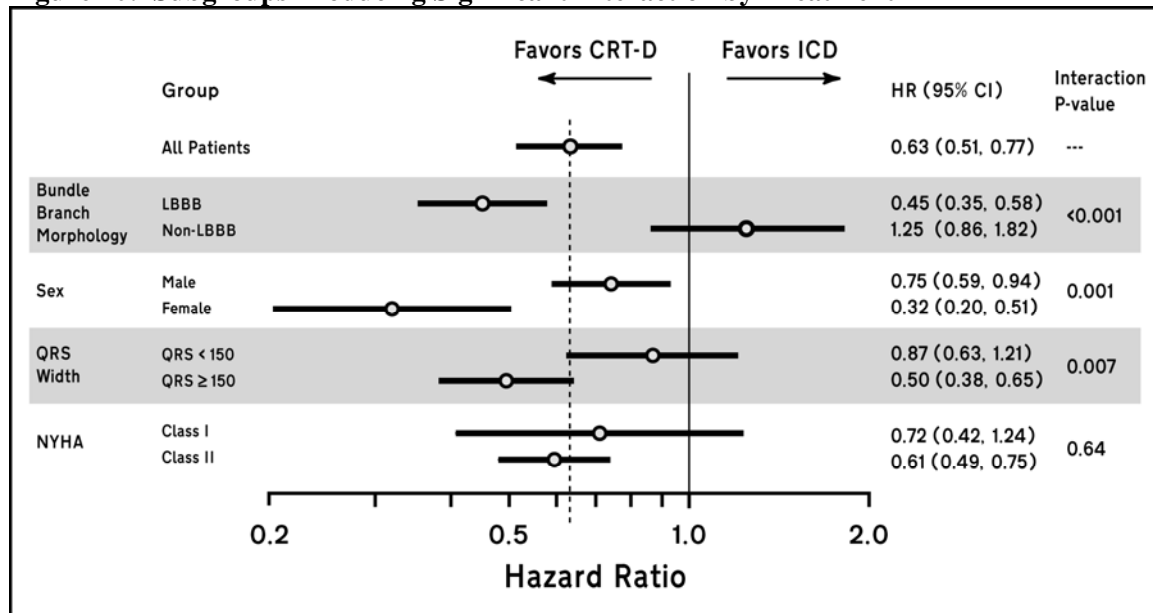
- Did the main study meet its primary endpoint? Significant improvement in the primary endpoint is necessary before further exploration of subgroups.
- Do statistically significant interactions exist? The presence of significant interactions by treatment and characteristic was a pre-condition for further consideration of that subgroup.
- Is the outcome biologically plausible? The results should have a physiologic basis for explaining the observed outcome.
- Are the results internally consistent? Similar results across other subgroups as well as corroboration from other outcome measures within the study can complement the findings and support the conclusion
- Are the results externally consistent? Independent corroboration of the results from other studies help strength the conclusions.

Fulfillment of these conditions in MADIT-CRT provided confidence that the results were valid and not a spurious finding.

Interaction Testing

Given the positive result of the primary effectiveness endpoint, and as pre-specified in the MADIT CRT statistical analysis plan, evaluation of varying CRT-D benefit by baseline characteristics was performed. Baseline characteristics that had a significant interaction with treatment in the primary endpoint were considered for further evaluation. The following three subgroups were identified: sex, QRS duration, and left bundle branch block (LBBB) as shown below in Figure 10. Other baseline variables examined that did not result in a significant interaction included NYHA Class, ischemic etiology, age, left ventricular volumes, and left ventricular ejection fraction. NYHA Class was also evaluated due to potential clinical importance.

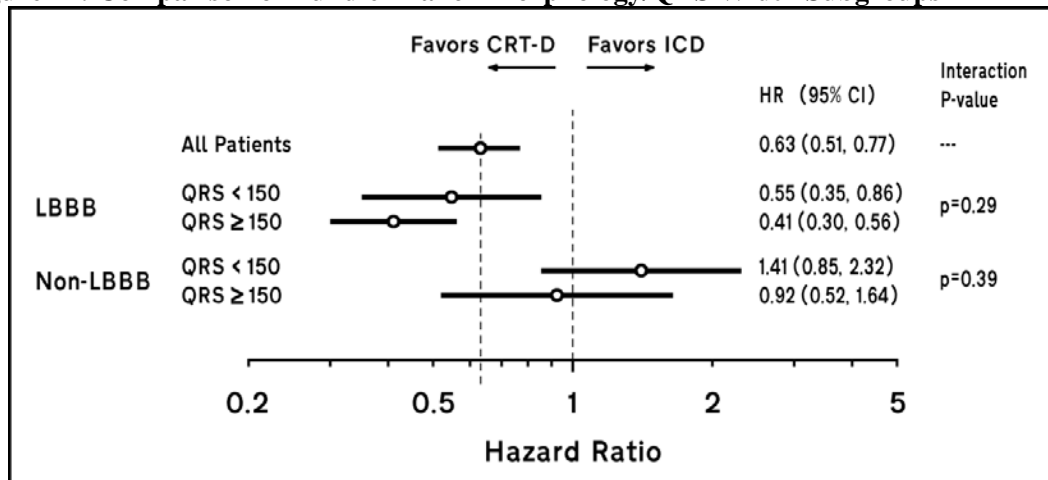
Figure 10: Subgroups Producing Significant Interaction by Treatment



A purpose of subgroup analyses is to identify which baseline characteristics differentiate CRT-D benefit. As shown above, CRT-D conferred benefit on both men and women, with women demonstrating enhanced benefit. Also, although not always statistically conclusive, CRT-D benefit was observed in both QRS width and NYHA Class subgroups. The only characteristic that clearly differentiated benefit was bundle branch morphology, suggesting that bundle branch morphology was the optimal baseline characteristic to differentiate which subgroup was most likely to benefit.

Aside from sex, which demonstrated CRT-D benefit in both sexes, bundle branch morphology and QRS width were the only other groups that demonstrated statistical and visual evidence of differentiating benefit. To further evaluate which subgroups best discriminated benefit, an analysis on whether QRS width and LBBB had a joint association with outcome or if one of these parameters alone sufficiently explained the results, was performed. The patient population was divided into four mutually exclusive groups based on these two subgroups as shown below in Figure 11.

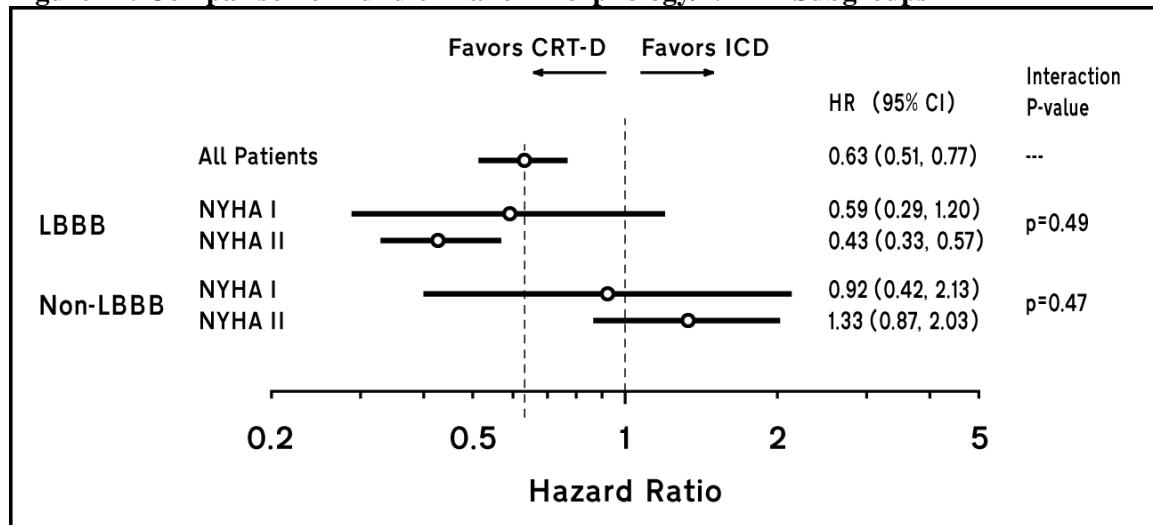
Figure 11: Comparison of Bundle Branch Morphology/QRS Width Subgroups



Visual inspection of Figure 11 suggested that LBBB, and not wider QRS, that best described the subgroup most likely to benefit. An interaction test that jointly considered treatment, LBBB, and QRS was conducted to verify this observation ($p=0.76$). A further interaction test in which treatment by QRS and treatment by LBBB were simultaneously tested in the same model demonstrated that only the LBBB interaction was significant ($p<0.001$) while the QRS by treatment, in contrast, was not significant ($p=0.14$). This outcome suggested that LBBB is a more significant differentiator of CRT-D benefit than QRS width. In addition, the influence of QRS within LBBB subgroups was not present, as shown in Figure 9 above ($p=0.29$ and $p=0.39$, respectively).

An additional population of interest as noted by FDA consisted of those patients with NYHA Class I. No treatment by NYHA Class interaction was found, as shown in Figure 12. Given that NYHA Class is a subjective measure that can fluctuate, left bundle branch block morphology as measured from a 12-lead ECG is an objective measure that more reliably identifies patients in whom CRT is effective.

Figure 12: Comparison of Bundle Branch Morphology/NYHA Subgroups



The statistical analysis led us to a preliminary conclusion that LBBB best identifies patients likely to benefit from CRT-D. Given the caveats of subgroup analysis, we considered additional clinical evidence to justify the identification of LBBB as a discriminator of CRT-D response.

Accordingly, the biological plausibility and internal/external consistency of these results were evaluated

Biologic Plausibility

Patients with left ventricular dysfunction may develop a dyssynchronous contraction such that the ventricular free wall(s) are not activated in a coordinated fashion with the septum. In LBBB, the septum contracts first against a left ventricular free wall that has not been activated. Once the left free wall has been activated, the septum has begun to relax. This asynchronous contraction is inefficient, reduces stroke volume, and increases the heart's workload⁽¹²⁾. With right bundle branch block (RBBB), it is right ventricular activation that is delayed and the right ventricular free wall contracts out of synchrony with the septum. Non-specific interventricular conduction delay (NS-IVCD) incorporates elements of delayed activation in both ventricles.

Longitudinal studies have suggested that LBBB is associated with a worsened mortality outcome when compared to RBBB and may itself contribute to left ventricular dysfunction⁽¹³⁾. Studies of

¹² Auricchio A et al. Circulation. 2004;109:1133-1139.

¹³ Lee SJ et al. J Card Failure 2003;9(2):87-92.

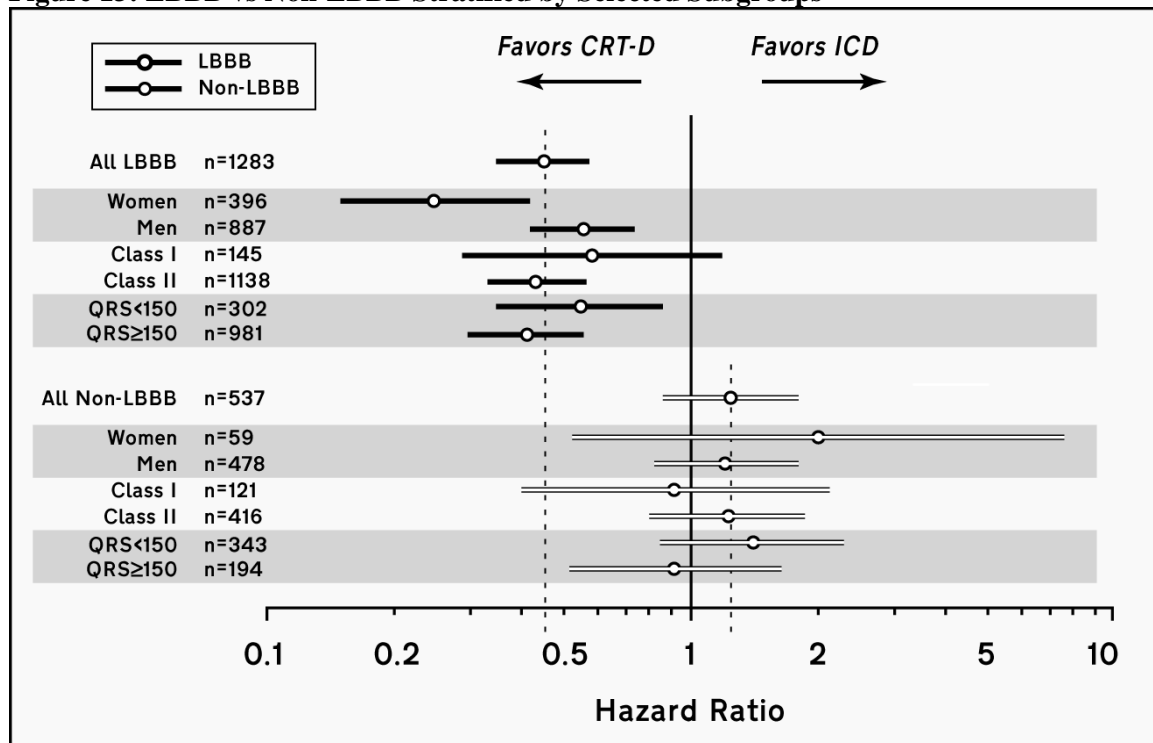
RBBB and LBBB with tagged magnetic resonance imaging (¹⁴) have found that while RBBB and LBBB are both associated with widened QRS and LV dysfunction, the mechanical dyssynchrony observed with RBBB was attenuated and was more similar to that of a normal heart. By comparison, the mechanical dyssynchrony associated with LBBB was more profound.

It therefore appears plausible that if the mechanism of action provided by CRT is to restore the activation sequence, it is more likely to be amenable in patients with LBBB since it is in these patients that dyssynchrony is most pronounced.

Internal Consistency

Bundle branch morphology not only differentiated CRT benefit across the entire population but also among several other subgroups as shown in Figure 13 below. Within the LBBB patients, benefit was demonstrated in patients with a QRS \geq 150 ms and QRS < 150 ms, as well as in NYHA Class II patients. The NYHA Class I patients show benefit that almost reaches statistical significance. Consistent with the full MADIT CRT population, both men and women demonstrated a benefit with CRT-D.

Figure 13: LBBB vs Non-LBBB Stratified by Selected Subgroups



¹⁴ Byrne MJ et al. J Am Coll Cardiol 2007;50:1484-90.

Other outcome variables examined are illustrated in Figure 14 and in Table 9. For event analyses, hazard ratios and confidence intervals are shown while echocardiographic parameters are expressed as mean change between CRT-D and ICD

Figure 14: Internal Consistency of LBBB Subgroup Across Multiple Outcomes

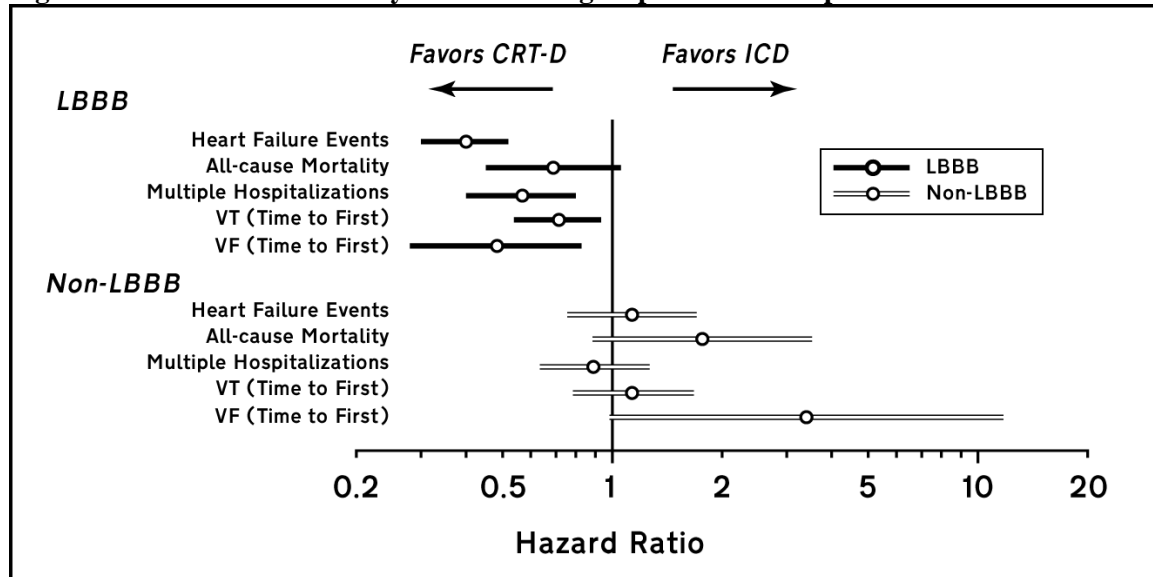


Table 9: Internal Consistency of LBBB Subgroup Across Echocardiographic Outcomes

Echocardiographic Parameter (Baseline to 12 Months)	LBBB CRT-D vs. ICD	Non-LBBB CRT-D vs. ICD
LVESV	-43 mL	-29 mL
LVEDV	-42 mL	-27 mL
LVEF	9%	6%

All echo changes were significant for CRT-D vs ICD at $p < 0.01$. Changes in echo parameters for the LBBB cohort were significantly greater than the non-LBBB patients ($p < 0.01$)

Within MADIT-CRT, LBBB was a robust parameter that differentiated improvement not only by the primary endpoint but across multiple outcomes and within multiple alternate subgroups as well. The benefit observed in LBBB patients appeared to be internally consistent.

External Consistency

Since MADIT-CRT is the first study of cardiac resynchronization therapy to demonstrate benefit in patients with asymptomatic or mild heart failure (NYHA Class I/II), there are no other published studies available for comparison. The REVERSE study results published subgroup

analyses but did not include bundle branch morphology in their overall results (¹⁵), the European (¹⁶) sub-population, or the echocardiography substudy (¹⁷).

Limited data are available for CRT in the NYHA Class III/IV population. Since heart failure has progressed to a more advanced stage in these patients, the ability to compare them to MADIT-CRT is limited.

Three randomized studies of CRT published their results in non-LBBB patients.

- Results from RBBB patients in the CONTAK CD and MIRACLE studies were pooled (¹⁸). Among clinical outcomes that included Peak VO₂, six minute walk, quality of life, and NYHA Class, no significant benefit was conferred by CRT.
- The primary endpoint of the COMPANION study (¹⁹) was a composite endpoint of all-cause mortality and all-cause hospitalization. No difference was observed between LBBB and non-LBBB patients.

Observational data from published single center experiences also suggests that LBBB is associated with improved outcome.

- Adelstein and Saba (²⁰) found greater improvement in symptoms and echocardiographic parameters among patients with LBBB. They also reported a lower all-cause mortality rate.
- Rickard et al (²¹) reported LBBB vs non-LBBB results in 355 patients receiving CRT and found that non-LBBB patients derived less symptomatic benefit and less reduction in volumes than LBBB patients. Unlike Adelstein and Saba, no difference was seen in mortality.

Published data to support external consistency in the same population as MADIT-CRT are limited. Results in a population with more severe heart failure suggest that LBBB patients may derive benefit from CRT but it is unknown whether other baseline characteristics provide superior performance.

¹⁵ Linde C et al. J Am Coll Cardiol 2008;52:1834-43.

¹⁶ Daubert C et al. J Am Coll Cardiol 2009;54(20):1837-46.

¹⁷ St John Sutton M et al. Circulation 2009;120:1858-65.

¹⁸ Egoavil CA et al. Heart Rhythm 2005;2:611-5.

¹⁹ Bristow MR et al. New Engl J Med 2004;350:2140-50.

²⁰ Adelstein EC and Saba S. Am J Cardiol 2009; 103:238-242.

²¹ Rickard J et al. Pacing Clin Electrophysiology 2009;1-6.

Subgroup Analysis Summary

MADIT-CRT demonstrated statistically significant improvement across patient population studied as a whole. Although there are limitations to subgroup analyses that should be considered, the biological plausibility and consistency of the data support the conclusion that LBBB morphology appeared to best identify those patients in MADIT-CRT who were most likely to derive benefit from CRT-D.

Risk/Benefit

In the MADIT-CRT trial, the incremental risk associated with implantation of a CRT-D system is more than outweighed by the observed benefit in decreasing the progression of heart failure status. The incremental risk is reflected in the incidence of system- related complications (SRCs) while the benefit is shown in the relative reduction in heart failure events (HFEs). Although the absolute rates of HFEs and SRCs over time were similar, we determined that the long-term sequelae associated with an HFE had a much greater impact on a patient's clinical status than those that were associated with an SRC.

It has been noted previously that once patients have heart failure events, a progressive decline in clinical status begins which is characterized by a predisposition towards additional heart failure events (²²). This tenet was a foundation for the philosophy behind the MADIT-CRT study, namely that CRT can materially slow the progression of heart failure by reducing the risk of HFEs.

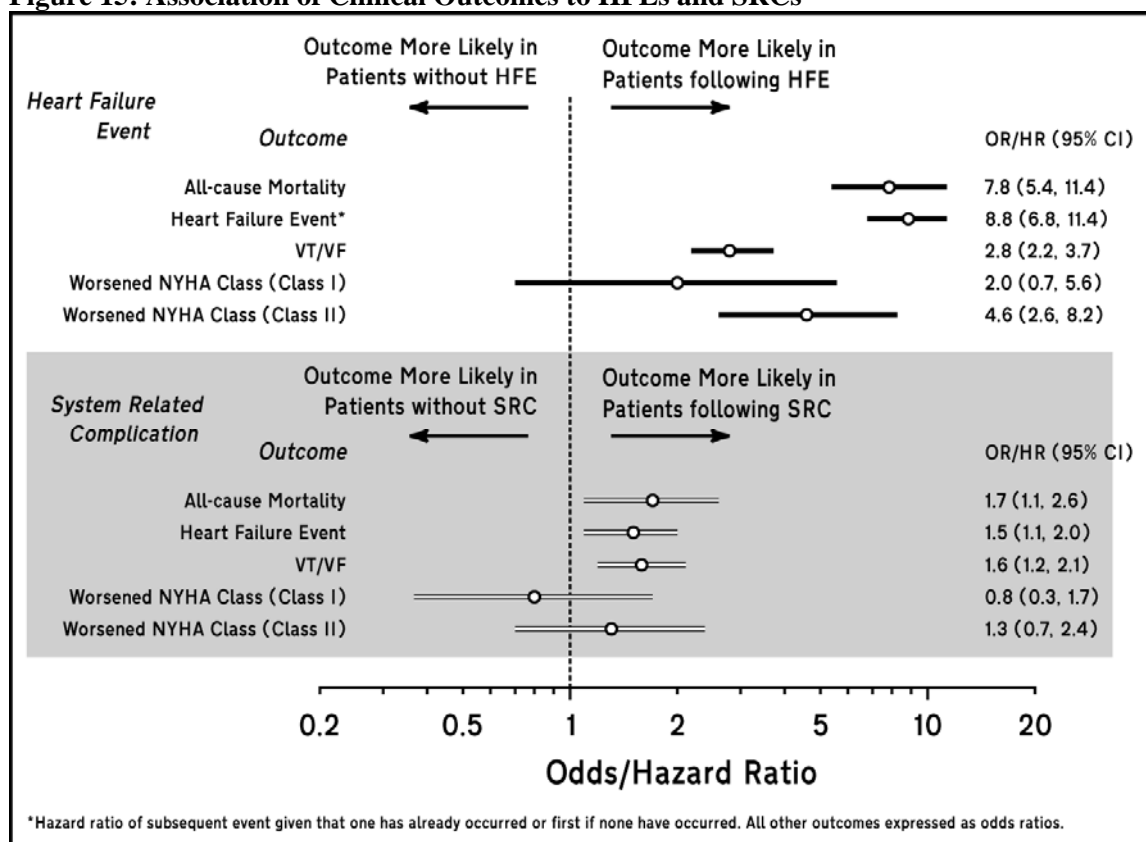
To evaluate the risks and benefits of CRT-D, the association between HFEs and important clinical outcomes were evaluated. For comparison purposes, the same analyses were done for SRCs. For each analysis, patients were divided into two cohorts: those who experienced an event (either HFE or SRC, depending on the analysis) and those who did not. These cohorts were evaluated for association with subsequent clinical outcomes (all-cause mortality, HF events, and VT/VF), NYHA class and quality of life.

The association between having an HFE (or SRC) with event-driven outcomes (all-cause mortality, HF events, and VT/VF) measured over the entire follow-up duration showed an eight-fold increase in the risk of having a subsequent event. Additional analyses based on changes in

²² Jain P et al. Am Heart J 2003;145:S3-S17.

NYHA Class during the first year of follow-up subsequent to an HFE (or an SRC) were performed. The prospect of worsened NYHA Class after 12 months was evaluated by comparing patients with/without an HFE and again for patients with/without an SRC. A computed odds ratio was used to determine whether or not these outcomes were associated with an HFE. The analysis was repeated to determine the effect of SRCs. The results are shown in Figure 15 below.

Figure 15: Association of Clinical Outcomes to HFEs and SRCs



The results from MADIT-CRT corroborate what has been reported in the medical literature. Although the absolute rates of HFEs and SRCs over time were similar, HFEs were associated with a greater negative impact on long-term outcomes than SRCs.

Patients were more likely to see a worsening in their symptomatic status (NYHA functional class) following an HFE when compared to those patients without an HFE, as shown above in Figure 14, which is consistent the analysis of event-driven outcomes. This difference was particularly acute in patients with NYHA Class II at baseline. Patients who experienced an SRC, by contrast, were unaffected and were not as likely to see worsened symptoms.

A further evaluation of long-term sequelae was based on the Kansas City Cardiomyopathy Questionnaire's (KCCQ) Overall Summary Score. The KCCQ is a valid, reliable and responsive health status measure specifically for patients with CHF and may serve as a clinically meaningful outcome measure. For this reason, it was chosen to evaluate MADIT-CRT patient assessment of well-being.²³ Quality of life based on the 12 month visit as well as the last visit to measure the impact over the entire follow-up duration based upon whether or not the patient had an HFE was examined. The analysis was repeated based upon whether or not the patient had an SRC. The results are shown in Table 10.

Table 10: Association of KCCQ Overall Summary Score to HFEs and SRCs

Outcome	Group	
	HFE	SRC
Change in Overall Summary Score (12 months)	-7.5* (-4.8, -10.2)	+0.3 (-1.7, 2.3)
Change in Overall Summary Score (last visit)	-11.3* (-9.5, -13.3)	-1.9** (-0.05, -3.8)

*Significant at p<0.001; **Significant at p<0.05

Similar to what has been seen for event-driven outcomes and symptomatic status, it was found that quality of life was negatively impacted by HFEs in a manner that was not observed for SRCs.

This analysis shows that HFEs are strongly associated with worsened outcomes while SRCs are not. SRCs tend to occur early, either during the implant procedure or shortly post implant and their likelihood of appearing long-term is low. The most common types of SRCs include events such as lead dislodgments or hematomas. While these events may require or extend a hospitalization, it is relatively easy to reposition a lead or evacuate a hematoma. These events are transient and unlikely to adversely affect patient outcomes beyond the event itself. HFEs, on the other hand, can occur at any time during follow-up and require significant resources to monitor and manage the patient during the hospital stay. Furthermore, the occurrence of HFEs was associated with greater rates of other untoward clinical outcomes, including more HFEs, which can contribute to a vicious cycle of worsened prognosis for heart failure patients.

The benefits associated with the MADIT-CRT study are striking. HFEs are associated with worsened outcomes across multiple clinical metrics in a way that is not echoed by SRCs. These

²³ Green, CP et al. J Am Coll Cardiol, 2000;35:1245-1255

supplemental analyses underscore the importance of reducing heart failure hospitalizations, which was the primary goal of the MADIT-CRT study.

Conclusion

MADIT-CRT is the only randomized clinical trial to demonstrate the safety and effectiveness of CRT-D devices in slowing the progression of heart failure in NYHA Class I ischemic and NYHA Class II ischemic and non-ischemic patients with low ejection fraction and wide QRS duration. The results from the pre-specified endpoints were successful and consistent across all secondary objectives and subgroups. A risk benefit analysis clearly indicates that the long term benefit of implanting a Boston Scientific CRT-D system outweighs any incremental risk. We therefore seek approval for an expanded indication for Boston Scientific CRT-D systems in this patient population.

Post Approval Study

Background

MADIT-CRT was the first trial to demonstrate a clinical benefit of CRT-D in patients with left ventricular dysfunction who do not exhibit symptoms of advanced heart failure (HF). The study showed a significant 34% ($p < 0.001$) relative reduction in the risk of a first HF event or all-cause mortality in NYHA Class I and II patients with a reduced ejection fraction and a prolonged QRS duration. The benefit of CRT-D in the trial was driven by a significant 41% relative reduction in the risk of a first HF event. Furthermore, the primary results demonstrated striking reduction in left ventricular volumes and improvement in left ventricular ejection fraction (LVEF).

A post-approval study in a MADIT-CRT patient population will evaluate additional benefits of CRT-D that may not have been demonstrated during the trial, including a mortality reduction, further reductions in the risk of heart failure progression, stabilization of NYHA functional class, and possible long-term benefits in patient subsets in whom CRT-D was associated with a less pronounced effect during the trial. Furthermore, the difference in CRT-D benefit between the sexes seen in the MADIT-CRT study will be evaluated for sustainability. Accordingly, the proposed follow-up study is designed to provide an assessment of the long-term benefits of CRT-D implantation in a MADIT-CRT patient population.

Study Design

The MADIT-CRT post-approval study would be an observational study consisting of a registry of a maximum of 585 patients implanted with a commercially available Boston Scientific CRT-D system. All MADIT-CRT active US patients implanted with a CRT-D (currently n=585) will be approached to participate in the post-approval study to leverage their implant and follow-up experience with CRT-D from the study (mean follow-up time 2.2 years as of 2/1/10 in the population of 585 CRT-D study patients); all patients would be followed for a total of five years. This would result in a registry that would last approximately four additional years.

We do not propose including those patients randomized to ICD as we may not be able to make meaningful comparisons between the therapies because of the anticipated loss of the ICD “control” arm to battery replacements and system upgrade to CRT-D as a result of an expanded CRT-D indication.

Approach

Primary Aims

1. To determine the long-term effect of CRT-D on all-cause mortality

Due to the relatively low mortality of the patients enrolled in MADIT-CRT (3% per year), the study was not powered to identify a statistically significant effect of CRT-D on the end point of all-cause mortality. However, analysis of the trial data demonstrates nearly a 16-fold increase in the risk of death following a first HF event among study patients (adjusted HR = 16 [95%CI 8 - 33]; $p < 0.001$). Thus, it is likely that the significant 41% reduction in the risk of a first HF event among CRT-D patients will translate into a significant mortality benefit during long-term follow-up. This information will have important implications regarding the long-term beneficial effects of device usage in lower-risk HF patients.

2. To evaluate the long-term benefit of CRT-D on the risk of heart failure progression in mildly symptomatic patients with left ventricular dysfunction

The significant reduction in the risk of first HF events during MADIT-CRT and the substantial improvement in LV volumes at 12 months of follow-up suggest that treatment with CRT-D may have important long-term implications for the prevention of HF progression in mildly symptomatic patients with left ventricular dysfunction, including (1) an incremental and sustained reduction in the risk of HF events among patients who

did not experience a HF event during the trial; (2) reduction in the risk of recurrent HF events with CRT-D among patients who experienced a first event during the trial; (3) stabilization of HF functional class during long-term follow-up. It is important to note that follow-up for subsequent HF events (i.e. after the occurrence of a first HF event) during the trial was limited to just over 1 year (14 months) on average. Therefore, a longer follow-up is likely to facilitate a comprehensive analysis of the benefit of CRT-D on the risk of recurrent HF events and stabilization of HF function class.

3. To determine the long-term effects of treatment with CRT-D in patients subsets

The primary results of MADIT-CRT suggest significant differences in the benefit of CRT-D in patient subsets (including important sex differences in the response to CRT-D). Long-term data regarding mortality and HF events are likely to demonstrate a further benefit in patients who exhibited Class I symptoms at baseline, and will provide important information regarding the long-term benefit of CRT-D in patient subsets who exhibited a less favorable response during the trial.

Methods

1. Data would be acquired at 6-month follow-up visits by a study coordinator. Data related to mortality, adjudicated heart failure events, NYHA Class and six-minute walk would be collected. The American College of Cardiology National Cardiovascular Data Registry (NCDR) will be used to collect acute implant complications and death to assess safety over time. All adverse events will also be collected.
2. Data management would be conducted by the Heart Research Follow-Up Program at the University of Rochester Medical Center, and data would be assessed at biannual intervals.

Statistical Analysis

End Points

Primary aim 1: Risk of all-cause mortality during long-term follow-up

Primary aim 2:

1. Risk of all-cause mortality or a heart failure event during long-term follow-up (HF hospitalization or outpatient treatment with IV diuretics)
2. Risk of recurrent HF events

3. Risk of advancing to NYHA functional class >II during follow-up
4. Six-minute walk

Post-Approval Study Summary

Upon conclusion of the panel, the sponsor looks forward to working with FDA to reach an agreement on a reasonable design to support the post-market study plan, and align with any remaining clinically relevant unanswered questions.