SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Cardiac Resynchronization Therapy Defibrillator (CRT-D)
Device Trade Name:	Cognis Cardiac Resynchronization High Energy Defibrillator Models N118, N119 (*P010012/S165, approved 5/08/2008*) Livian Cardiac Resynchronization Therapy Defibrillators Models H220, H225, H227 and H229 (*P010012/S154, approved 2/15/2008*) Contak Renewal 3 RF HE CRT-D Models H210, H215, H217, H219 (*P010012/S031, approved 2/09/2005*)
Applicant's Name and Address:	Guidant Corporation, a wholly-owned subsidiary of Boston Scientific Corporation, Cardiac Rhythm Management 4100 Hamline Avenue North St. Paul, Minnesota 55112-5798

Date of Panel Recommendation: March 18, 2010

Premarket Approval Application (PMA) Number: P0100012 / S230

Date of FDA Notice of Approval: September 16, 2010

Expedited: Granted expedited review status on January 11, 2010, because the device provides a specific public health benefit or meets the need of a well-defined patient population

The original PMA P010012, Contak CRT-D, was approved on May 2, 2002, and is indicated for:

> patients who are at high risk of sudden cardiac death due to ventricular arrhythmias and who have moderate to severe heart failure (NYHA Class III/IV) including left ventricular dysfunction (EF $\leq$ 35%) and QRS duration $\geq$ 120 ms and remain symptomatic despite stable, optimal heart failure drug therapy.
>
> Patient populations at high risk of sudden cardiac death due to ventricular arrhythmias include, but are not limited to, those with:
>
> - Survival of at least one episode of cardiac arrest (manifested by the loss of consciousness) due to a ventricular tachyarrhythmia.

- Recurrent, poorly tolerated sustained ventricular tachycardia (VT).

  NOTE: The clinical outcome of hemodynamically stable, sustained-VT patients is not fully known. Safety and effectiveness studies have not been conducted.

- Prior myocardial infarction, left ventricular ejection fraction of ≤ 35%, and a documented episode of nonsustained VT, with an inducible ventricular tachyarrhythmia. Patients suppressible with IV procainamide or an equivalent antiarrhythmic (drug) have not been studied.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here.

PMA supplement P010012 / S014, (Contak CD, Contak CD 2, Renewal, Renewal 3), was approved on October 21, 2003, and the indication stated above was further expanded to include:

- Patients who may benefit from prophylactic treatment due to a prior myocardial infarction and an ejection fraction ≤ 30%.

PMA supplement P010012 / S017, (Ventak AV, Prizm, Vitality, Vitality AVT, Ventak PRx, Ventak Mini, Contak CD, Renewal), was approved on February 6, 2004, and the indications were changed to:

Guidant (BSC) cardiac resynchronization therapy defibrillators (CRT-Ds) are intended to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. Guidant CRT-Ds are also indicated for reduction of symptoms of moderate to severe heart failure (NYHA III/IV) in patients who remain symptomatic despite stable, optimal heart failure drug therapy, and have left ventricular dysfunction (EF ≤ 35%) and QRS duration ≥ 120 ms.

PMA supplement P010012 / S026, (Contak CD, Contak CD 2, Renewal, Renewal 3), was approved on September 14, 2004, and the indications were changed to:

Guidant (BSC) cardiac resynchronization therapy 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 ≤ 35%) and QRS duration ≥ 120 ms.

The current supplement was submitted to expand the indications for use for the Cognis, Livian, and Contak Renewal 3 RF HE CRT-D's to include patients with left bundle branch block (LBBB) with QRS ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure

II. INDICATIONS FOR USE

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

- Moderate to severe heart failure (NYHA Class III-IV) with EF ≤ 35% and QRS duration ≥ 120 ms

- Left bundle branch block (LBBB) with QRS ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure

III. CONTRAINDICATIONS

There are no contraindications for this device.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Cognis, Livian, and Contak Renewal 3 RF HE labeling (System Guide).

V. DEVICE DESCRIPTION

There were no changes to the device description as compared to the previously approved devices. The following paragraphs provide a brief description of the devices.

These devices are implantable pulse generators, designed to sense electrical activity and to deliver electrical pulses. These devices are commonly referred to as implantable cardioverter defibrillators (ICD) that also delivery cardiac resynchronization therapy (CRT) and are commonly refer to as CRT-D (cardiac resynchronization therapy defibrillators). These devices provide ventricular tachyarrhythmia and cardiac resynchronization therapies. Ventricular tachyarrhythmia therapy is for the treatment of ventricular tachycardia (VT) and ventricular fibrillation (VF), rhythms that are associated with sudden cardiac death (SCD). Cardiac resynchronization therapy is for the treatment of heart failure (HF) and uses biventricular electrical stimulation to synchronize ventricular contractions. The devices also use accelerometer-based adaptive-rate bradycardia therapy. The pulse generators accept one IS-1 atrial lead, one LV-1 or one IS-1 coronary venous pace/sense lead, and one DF-1/IS-1 cardioversion / defibrillation lead.

Cardioversion/defibrillation therapies include a range of low- and high-energy shocks using either a biphasic or monophasic waveform. The devices use the Triad electrode system for defibrillation energy delivery. By using the metallic housing of the pulse generator as an active electrode, combined with a two-electrode defibrillation lead, energy is sent via a dual-current pathway from the distal shocking electrode to the proximal electrode and to the pulse generator case. The devices also offer a wide variety of antitachycardia pacing schemes to terminate slower, more stable ventricular tachyarrhythmias. Bradycardia pacing with cardiac resynchronization therapy, including adaptive-rate features, is available to detect and treat bradyarrhythmias and to support the cardiac rhythm after defibrillation therapy.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of heart failure patients who have left ventricular dysfunction. These patients are routinely treated with medications. Medications may include those to treat arrhythmias as well as medications to treat heart failure. Additional medical treatments for heart failure include, but are not limited to, exercise and nutrition programs. Alternative therapies for treatment of ventricular arrhythmias, as deemed appropriate by the physician based upon electrophysiological testing and other diagnostic evaluation, include antiarrhythmic medication, electrical ablation, cardiac surgery, and electronic devices including pacemakers and other legally marketed implantable cardioverter defibrillators (ICD) systems, or a combination thereof.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Boston Scientific's Cognis, Livian, and Contak Renewal 3 RF HE CRT-Ds are currently available for commercial distribution in the U.S. and other countries including: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Dominican Republic, Finland, France, Germany, Greece, Guadeloupe, Guyana, Hong Kong, Iceland, India, Indonesia, Ireland, Israel, Italy, Jordan, Kuwait, Lebanon, Liechtenstein, Luxembourg, Malaysia, Martinique, Netherlands, New Caledonia, New Zealand, Norway, Portugal, San Marino, Saudi Arabia, Singapore, Slovenia, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, United Kingdom, and Venezuela. As of August 4, 2010, no Cognis, Livian, or Contak Renewal 3 RF HE CRT-Ds are currently withdrawn for safety issues from the market in any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., observations and complications) associated with the use of the devices.

The potential risks related to this study include those typical of implantation of a CRT-D system and those associated with the protocol. Based on published literature and pacemaker/lead implant experience, the following list includes possible physical effects from implantation of a CRT-D system:

- Air embolism
- Allergic reaction (e.g. titanium)
- Bleeding
- Cardiac tamponade
- Chronic nerve damage
- Component failure
- Conductor coil fracture
- Death
- Electrolyte imbalance/dehydration
- Elevated thresholds
- Erosion
- Excessive fibrotic tissue growth
- Extracardiac stimulation (muscle/nerve stimulation)
- Failure to convert an induced arrhythmia
- Foreign body rejection phenomena
- Formation of hematomas or seromas
- Inability to defibrillate or pace
- Inappropriate therapy (e.g., shocks where applicable, ATP, pacing)
- Incisional pain
- Incomplete lead connection with pulse generator
- Infection
- Insulating myocardium during defibrillation with internal or external paddles
- Lead dislodgment
- Lead fracture
- Lead insulation breakage or abrasion
- Lead tip deformation and/or breakage
- Myocardial infarction (MI)
- Myocardial necrosis
- Myocardial trauma (e.g., cardiac perforation, irritability, injury)
- Myocardial sensing
- Oversensing/undersensing
- Pacemaker-mediated tachycardia (PMT)
- Pericardial rub, effusion
- Pneumothorax
- Pulse generator migration
- Shunting current during defibrillation with internal or external paddles

- Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
- Thrombosis/thromboemboli
- Valve damage
- Venous occlusion
- Venous trauma (e.g. perforation, dissection, erosion)
- Worsening heart failure

Patients may develop psychological intolerance to a pulse generator system that may include the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking

In addition to the implantation of a pulse generator system, potential adverse events associated with implantation of a coronary venous lead system include:

- Allergic reaction to contrast media
- Breakage/failure of implant instruments
- Prolonged exposure to fluoroscopic radiation
- Renal failure from contrast media used to visualize coronary veins

These risks can be minimized through use of strict aseptic technique, compliance with technical implant procedures, adherence to the guidelines for selection of subjects, and close monitoring of the subject's physiologic status during the implant and follow-up procedures.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

The Cognis, Livian, and Renewal 3 RF HE CRT-D's are commercially available systems. These systems were previously evaluated via non-clinical laboratory testing including bench testing (including hardware/software verification and validation), biocompatibility testing, and animal studies. Device design and system compatibility involved verification and validation of the system. The test procedures and results were previously reviewed and approved.

These issues were reviewed in previous submissions as follows:

- Cognis Cardiac Resynchronization High Energy Defibrillator Models N118, N119 (P010012/S165, approved 5/08/2008)
- Livian Cardiac Resynchronization Therapy Defibrillators Models H220, H225, H227 and H229 (P010012/S154, approved 2/15/2008)
- Contak Renewal 3 RF HE CRT-D Models H210, H215, H217, H219 (P010012/S031, approved 2/09/2005)

X. SUMMARY OF PRIMARY CLINICAL STUDY

Boston Scientific sponsored the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) clinical study to demonstrate the safety and effectiveness of Boston Scientific CRT-Ds in heart failure patients with QRS $\geq$ 130 ms, EF $\leq$ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure. MADIT-CRT was a prospective, randomized, controlled, global multicenter study conducted at 110 investigational centers.

The primary safety and effectiveness endpoints were met. The primary effectiveness endpoint demonstrated a statistically significant reduction in the combined endpoint of all-cause mortality and heart failure events in the CRT-D group as compared to the ICD group. This reduction was driven entirely by heart failure events; there was no difference in mortality between the groups. The results were also analyzed by various subgroups that were pre-specified by the sponsor at the onset of the trial. However, an additional analysis, which was not pre-specified, looked at the subgroup of patients with left bundle branch block (LBBB) morphology on their ECG as compared to non-LBBB patients (including right bundle branch block (RBBB) and non-specific interventricular conduction delay).

Although the analysis of LBBB was post-hoc, the results were consistent across a variety of other demographic and clinical variables. In addition, the subgroup analysis of patients with LBBB was compelling and consistent with previous observations regarding LBBB and cardiac resynchronization therapy. LBBB patients had a greater reduction in heart failure events as compared to non-LBBB patients. Further discussions resulted in a restriction in the final indications for use to those patients with LBBB. As a result, the following clinical summary refers to both the full MADIT-CRT population and to the cohort of LBBB patients enrolled in the MADIT-CRT clinical study. Additional information about the rationale for this restriction to LBBB patients is provided in both the advisory panel and conclusion sections of this document.

A total of 1820 patients were enrolled and randomized in a 3:2 ratio to receive CRT-D (1089) or ICD (731). Of the 1820 patients, 1281 (70.4%) had LBBB; 761 received CRT D and 520 received ICD. Randomization was stratified by clinical center and ischemic status. Each randomized patient remained counted as a member of the original randomized assignment (intention-to-treat) regardless of subsequent crossover or protocol adherence.

A. Study Design

Patients were implanted from December 22, 2004 through April 23, 2008. The database for this PMA supplement reflected data collected through December 31, 2009 and included 1820 patients. There were 110 investigational sights.

MADIT-CRT was a prospective, multi-center, randomized clinical study conducted in the United States (US), Europe, Canada, and Israel. Patients were randomized in a 3:2 ratio to receive either a CRT-D or implantable cardioverter defibrillator (ICD). Randomization was stratified by clinical center and ischemic status.

The study design was a Wang-Tsiatis group-sequential design, with two-sided significance level of 5% with 95% power to detect a hazard ratio of 0.75. The study was designed to allow for one of the following conclusions (A) CRT-D is superior, (B) ICD is superior, or (C) there is no real difference between the two treatment regimens. However, this design did not allow early stopping for a conclusion of no difference.

MADIT-CRT used an Executive Committee, Data Safety Monitoring Board (DSMB), Heart Failure Event Committee, and Mortality Event Review Committee (MERC) for study strategy, safety, heart failure event adjudication, and mortality adjudication, respectively.

Data continued to be collected and events were adjudicated until December 31, 2009.

1. Clinical Inclusion and Exclusion Criteria

Inclusion Criteria

Patients who met the following inclusion criteria were given consideration for inclusion in the MADIT-CRT clinical investigation:

- NYHA Class I or II patients for the three calendar months prior to and at the time of enrollment with ischemic heart disease defined as:
- one or more clinically documented (q wave or enzyme positive) prior myocardial infarction, but not within three calendar months of enrollment *and/or*
- one or more prior coronary artery bypass graft surgeries or percutaneous coronary intervention (balloon and/or stent angioplasty), but not within three calendar months of enrollment;

OR

- NYHA Class II patients for the three calendar months prior to and at the time of enrollment with non-ischemic heart disease defined as including dilated cardiomyopathy characterized by a low ejection fraction and increased ventricular volume, with ventricular compliance that is normal or increased;

AND all of the following:

- Stable Optimal Pharmalogical Therapy (OPT) (including ACEs (Angiotensin Converting Enzymes) / ARBs (Angiotensin Receptor blockers), Beta Blockers Diuretics). Ischemic patients were required to have statin therapy.
- An ejection fraction ≤ 0.30 by angiographic, radionuclide, or echocardiographic methods within one year prior to enrollment and measured during the enrollment echocardiogram
- Resting QRS duration ≥ 130 ms on print-out of a current ECG using a market-approved electrocardiographic recorder
- Sinus rhythm by ECG (including RBBB and first degree heart block with PR< 250 ms.)
- Men and women 21 years of age or older (no upper-age cut off)

Exclusion Criteria

Patients were excluded from the MADIT-CRT clinical investigation if any of the following conditions applied:

- Existing indication for CRT therapy
- Implanted pacemaker
- Existing ICD or CRT device
- NYHA Class I with non-ischemic cardiomyopathy
- NYHA Class III or IV in the past three calendar months prior to or at the time of enrollment
- Coronary artery bypass graft surgery or percutaneous coronary intervention (balloon and/or stent angioplasty) within the past three calendar months prior to enrollment
- Enzyme-positive myocardial infarction within the past three calendar months prior to enrollment
- Angiographic evidence of coronary disease who were candidates for coronary revascularization and are likely to undergo coronary artery bypass graft surgery or percutaneous coronary intervention in the foreseeable future
- Second or third degree heart block
- Irreversible brain damage from preexisting cerebral disease
- Pregnant or plan to become pregnant during the course of the study (Note: Women of childbearing potential must have had a negative pregnancy test within 7 days prior to enrollment)
- Reversible non-ischemic cardiomyopathy such as acute viral myocarditis or discontinuation of alcohol in alcohol-induced heart disease
- Chronic atrial fibrillation within one month prior to enrollment
- Presence of any disease, other than the patient's cardiac disease, associated with a reduced likelihood of survival for the duration of the study, e.g., cancer, uremia (BUN>70mg/dl or creatinine >3.0mg/dl), liver failure, etc
- Participating in any other clinical studies
- Unwilling or unable to cooperate with the protocol

- Live at such a distance from the clinic that travel for follow-up visits would be unusually difficult
- Did not anticipate being a resident of the area for the scheduled duration of the study
- Unwilling to sign the consent for participation

2. Follow-up Schedule

In the MADIT-CRT study 1820 patients were randomized to CRT-D or ICD and enrolled between December 22, 2004 and April 23, 2008. Table 1 provides a summary of the follow-up timeline and procedures performed.

Table 1: Follow-Up Schedule

Follow-Up	Description
Screening	Initial assessment of patient eligibility; taking of patient history
Pre-randomization confirmation testing	ECG and echocardiogram
Randomization	Randomization status (CRT-D or ICD) was assigned
Baseline Testing	Six-minute walk, Holter, QoL, BNP (US only)
Routine clinic follow-ups	1, 3, and every 3 months
Special testing	Echocardiogram, 6-minute walk, Holter, BNP (US only), QoL (every 6 months)

As of December 31, 2009, the total patient follow-up months were 62,335 months: 24,683 in the ICD group and 37,653 in the CRT-D group. The mean follow up duration was 34.3±12.2 months; 33.8±12.9 months in the ICD arm and 34.6±11.7 months in the CRT-D arm. There was no statistically significant difference in the follow-up duration between treatment arms. The follow-up duration details are summarized below in Table 2.

Table 2: Follow-up Duration (all patients randomized, N=1820)

Measurement	Follow-up Duration (months)	ICD (N = 731)	CRT-D (N = 1089)
Mean ± SD	34.3 ± 12.2	33.8 ± 12.9	34.6 ± 11.7
Range	0.03 - 58.97	0.03 - 58.94	0.03 - 58.97
Total Patient Months	62,335	24,683	37,653

3. Clinical Endpoints

Primary Study Objectives

Safety Endpoint: Determine if the CRT-D system-related complication-free rate observed was greater than 70% after three months of follow-up post-implant

Primary Effectiveness Endpoint: Determine whether CRT-D resulted in a statistically significant reduction in the combined endpoint of all-cause mortality or heart failure event, whichever came first, when compared to ICD.

All deaths were reviewed and adjudicated by the Mortality Event Committee. All heart failure events were reviewed and adjudicated by the Heart Failure Event Committee and the members were blinded to the randomized therapy.

Additional Objectives

Secondary: Evaluate the effects of CRT-D, relative to ICD, on the patient-specific rates of recurrent heart failure events over the full study period.

Tertiary: Evaluate the effects of CRT-D on:

- All-cause mortality
- Appropriate defibrillator therapy for ventricular tachycardia (VT) and/or ventricular fibrillation (VF)
- Changes in echocardiographic structure and function at 12 months (echo-determined left ventricular internal volume at end-systole and diastole (LVESV and LVEDV) and changes in LVEF at 12 months)
- Changes in NYHA functional class at 12 months
- Changes in quality of life at 12 months and over the full study period
- Mitral regurgitation at 12 months
- Functional capacity (six minute hall walk) at 12 months
- The association between BNP and outcome with CRT-D
- Brain natriuretic peptide (BNP) levels at 12 months
- Holter-recorded electrocardiographic parameters and hemodynamic response

Safety Endpoint

The MADIT-CRT study assessed the CRT-D safety by the system-related complication-free rate observed within the date of implant and three months of follow-up. For the purposes of the safety analysis, three month follow-up was defined as 91 days post-implant.

Hypothesis:

H_o: The system-related complication-free rate $\leq 70\%$

H_a: The system-related complication-free rate $> 70\%$.

Primary Effectiveness Endpoint

The MADIT-CRT study assessed the effectiveness of CRT-D by the relative reduction of the risk of the combined endpoint of all-cause mortality or HF event, whichever occurred first, when compared to ICD.

The primary effectiveness analysis was based on comparing the Kaplan-Meier life-table event-free survival time graphs for the CRT-D and ICD groups. The stratified log-rank test (stratified by clinical center and ischemic status) was used to evaluate statistical significance, adjusting for the group-sequential stopping rule of the study.

Hypothesis:

H_o: The event-free survival curves for the combined endpoint of HF event or all-cause mortality do not differ between the ICD and CRT-D groups.

H_a: The event-free survival curve for the CRT-D group is above that for the ICD group, with a hazard ratio less than unity.

Secondary Endpoint

The MADIT-CRT study also evaluated the effects of CRT-D, relative to ICD, on the patient-specific rates of multiple HF events over the full study period.

Hypothesis:

H_o: The HF event rates do not differ between the ICD and CRT-D groups.

H_a: The HF event rate for the CRT-D group is less than that for the ICD group, with an average-rate ratio less than unity.

Tertiary Endpoints

The trial included ten tertiary, exploratory objectives as follows:

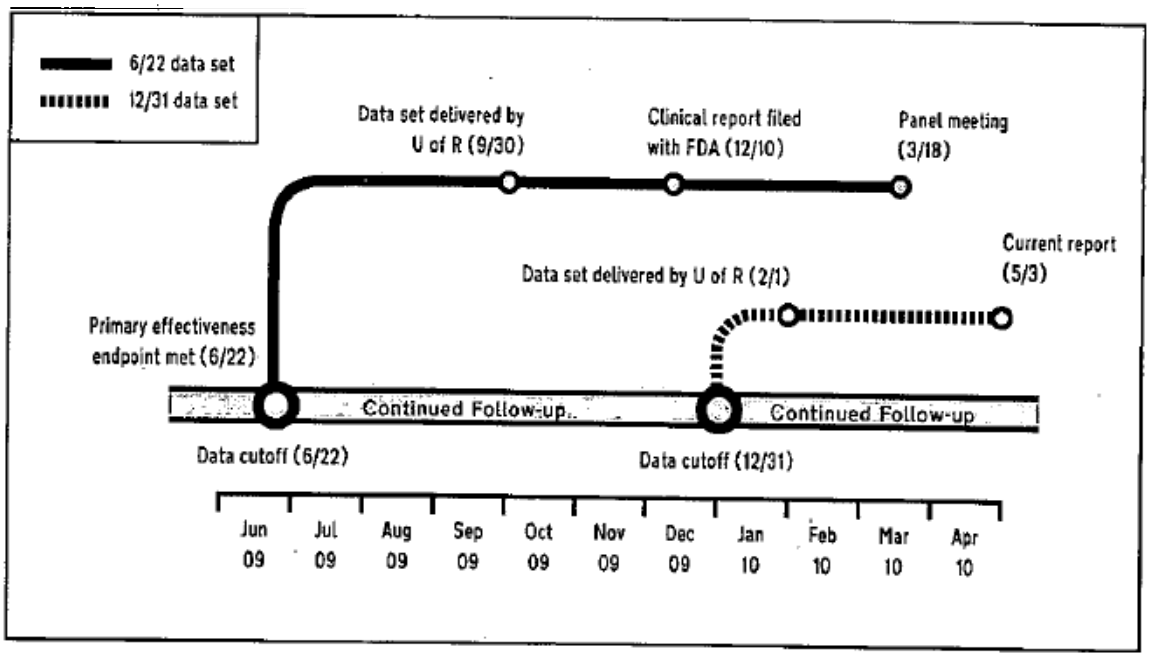
- Evaluate the effects of CRT-D on all-cause mortality.
- Evaluate the effects of CRT-D on appropriate ICD therapy for ventricular tachycardia (VT) and ventricular fibrillation (VF).
- Evaluate the effects of CRT-D, relative to ICD-only, on the changes from baseline to one year in ECHO-determined left ventricular internal volume at end systole (LVESV) and at end diastole (LVEDV).
- Evaluate the effects of CRT-D, relative to ICD-only, on the changes from baseline to one year in NYHA functional class. It is hypothesized that, at one year, the average NYHA class for the CRT-D group will be lower than that for the ICD-only group, after adjusting for any differences in baseline values.

- Evaluate the effects of CRT-D, relative to ICD-only, on the accumulated changes in quality-of-life within the full study period. It is hypothesized that the assessed quality of life in the CRT-D group will, on average, exceed that in the ICD-only group.
- Evaluate by echocardiographic/Doppler technique at the 12 month follow-up whether CRT-D when compared to subjects receiving ICD-only reduces the degree of mitral regurgitation (echocardiographic subprotocol).
- Evaluate whether functional capacity (as measured by distance achieved during a 6 minute hall walk) at the 12 month follow-up is greater in subjects receiving CRT-D than in those receiving ICD-only.
- Evaluate the association between the level of brain natriuretic peptide (BNP) at baseline and outcome in subjects randomized to CRT-D.
- Evaluate whether the level of brain natriuretic peptide (BNP) at the 12-month follow-up visit is lower in the CRT-D group than the ICD-only group.
- Evaluate whether Holter-recorded non-invasive parameters can identify subjects with increased hemodynamic benefit in CRT responders and non-responders.

B. Accountability of PMA Cohort

Two data sets were used in reporting MADIT-CRT results to FDA. The first was based on a data cutoff of June 22, 2009. At that time, Boston Scientific announced that the MADIT-CRT study met its primary effectiveness endpoint. Based on this data cutoff, a data set was delivered to the sponsor by the data coordinating center on September 30, 2009. A report was prepared and submitted to FDA on December 10, 2009. The results from this data set were also presented to the cardiovascular devices advisory panel on March 18, 2010.

Meanwhile, a second data set was created that updated the results with events that occurred on or before December 31, 2009. Heart failure events were adjudicated and a data set delivered to the sponsor on February 1, 2010 by the data coordinating center. These additional data have been incorporated and the results from the December 10, 2009 report have been updated. A timeline illustrating the timing of data cutoffs and significant events in the regulatory history are shown below.



C. Study Population Demographics and Baseline Parameters

Key information related to enrollment, patient demographics, and the primary endpoints is represented below in Table 3. Table 3 includes a brief summary of the demographics for both the full MADIT-CRT population and the MADIT-CRT LBBB sub-population. Tables 4 through 9 provide more detailed information about the full demographics of the randomized CRT-D and ICD groups from the full MADIT-CRT study, in order to provide a more complete picture of the original supporting study and to demonstrate the similarities of the two (2) randomized groups of patients.

Table 3: Demographic Data (All MADIT-CRT Patients and LBBB Patients)

Data Item	Result (All Patients)	Result (LBBB Only)
Number of enrolled patients	1820	1281
Number of randomized patients (CRT-D/ICD)	1089 / 731	761 / 520
Number of implanted patients (CRT-D/ICD)	1078 / 712	757 / 507
Number of attempted patients (CRT-D/ICD)	1 / 0	1 / 0
Number of intent patients (CRT-D/ICD)	10 / 19	3 / 13
Mean follow-up time (± SD)	34.3 ± 12.2 months	34.8 ± 12.3 months
Implant phase	01/05/05 - 05/05/08	01/05/05 - 05/05/08
Number of centers	110	109†
Patient Demographics	**Result**	**Result**
Gender	75 % Male 25 % Female	69 % Male 31 % Female

Data Item	Result (All Patients)	Result (LBBB Only)
NYHA Classification	15 % Class I Ischemic 40 % Class II Ischemic 45 % Class II Non-Ischemic	11 % Class I Ischemic 33 % Class II Ischemic 56 % Class II Non-Ischemic
Mean Age (± SD)	64 ± 11 years	64 ± 11 years
Mean LVEF (± SD)	24 ± 5 %	24 ± 5 %
Mean QRS (± SD)	158 ± 20 ms	163 ± 19 ms
Endpoint Summary	**Result**	**Result**
Primary Safety System-Related Complication Free Rate (Lower One-Sided 95% Confidence Bound)	84.8 (82.9)	83.4 (81.0)
Primary Effectiveness Hazard Ratio (95% Confidence Interval)	0.61 (0.50, 0.75); p<0.001*	0.43 (0.33,0.56); < 0.001*

† One (1) center enrolled no patients with LBBB morphology

* Hazard ratio adjusted for ischemic status and center

The general characteristics of the 1820 patients randomized in MADIT-CRT are presented in the following six tables (Tables 4 through 9) according to assigned randomization, including baseline demographics, cardiac history, cardiac risk factors, cardiac findings at enrollment, baseline echocardiographic volumes and cardiac medications. Patient characteristics were well-balanced between the therapy groups. 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±5% and a mean QRS of 158±20 ms. The majority of patients were 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.

Table 4: Baseline Demographics (all patients randomized, N=1820) - Full Patient Population

Characteristic	Measurement	ICD (N=731)	CRT-D (N=1089)	P-value
Age at Implant (years)	N	731	1089	
	Mean ± SD	64 ± 11	64 ± 11	0.74

Characteristic	Measurement	ICD (N=731)	CRT-D (N=1089)	P-value
	Range	32 - 88	25 - 90	
Gender [N (%)]	Female	178 (24.4)	275 (25.3)	0.66
	Male	553 (75.6)	814 (74.7)	
Race [N (%)]	White	658 (90.8)	980 (90.4)	
	Black/African American	56 (7.7)	87 (8.0)	0.97
	Other*	11 (1.5)	17 (1.6)	

* Other races include Asian, American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, and more than one race

Table 5: Cardiac History (all patients randomized, N=1820) - Full Patient Population

Characteristic	Measurement	ICD (N=731)	CRT-D (N=1089)	P-value
NYHA Class/Ischemic [N (%)]	Class I Ischemic	113 (15.5)	152 (14.0)	0.63
	Class II Ischemic	288 (39.4)	446 (41.0)	
	Class II Non-Ischemic	330 (45.1)	491 (45.1)	
Worst NYHA class > 3 mos prior to enrollment [N (%)]*	Class III/IV	73 (10.4)	109 (10.4)	0.99
Number of CHF Hospitalizations Prior to Enrollment [N (%)]	None	451 (63.3)	656 (61.3)	0.69
	1 – 2	231 (32.4)	365 (34.1)	
	3 or more	31 (4.3)	50 (4.7)	

* Patients who were Class I or II at enrollment but had prior history of Class III or IV more than 3 months prior to enrollment.

Table 6: Cardiac Risk Factors (all patients randomized, N=1820) - Full Patient Population

Risk Factor	ICD (N=731) [N (%)]	CRT-D (N=1089) [N (%)]	P-value
Treatment for Hypertension	461 (63.2)	691 (63.7)	0.82
Atrial fibrillation > 1 month before enrollment	90 (12.3)	118 (10.8)	0.33
Diabetes Mellitus	223 (30.6)	329 (30.2)	0.87
Cigarette Smoking	92 (12.8)	122 (11.4)	0.37
Body-mass index >= 30	256 (35.4)	378 (35.2)	0.95
Coronary-bypass surgery	208 (28.5)	317 (29.1)	0.77

Table 7: Cardiac Findings at Enrollment (all patients randomized, N=1820) – Full Patient Population

Characteristic	Measurement	ICD (N=731)	CRT-D (N=1089)	P-value
Conduction	LBBB [N (%)]	520 (71.3)	761 (69.9)	0.51
	RBBB [N (%)]	92 (12.6)	136 (12.5)	0.93
	IVCD [N (%)]	111 (15.2)	182 (16.7)	0.40
Systolic Blood Pressure (mm Hg)	N	719	1074	
	Mean ± SD	121 ± 18	124 ± 17	0.001*
	Range	80 - 193	78 - 194	
Diastolic Blood Pressure (mm Hg)	N	719	1074	
	Mean ± SD	71 ± 10	72 ± 10	0.002*
	Range	37 - 107	40 - 110	
BUN (blood urea nitrogen) >= 26 mg/dL	N (%)	173 (24.0)	254 (23.5)	0.79
Creatinine (mg/dl)	N	725	1083	
	Mean ± SD	1.2 ± 0.4	1.2 ± 0.4	0.51
	Range	0.5 - 7.2	0.4 – 5.6	
QRS duration >= 150 ms	N (%)	476 (65.1)	699 (64.2)	0.68
LVEF (%)	N	731	1089	
	Mean ± SD	24 ± 5	24 ± 5	0.33
	Range	6 - 32	7 – 35	
BNP (pg/ml)	N	473	724	
	Mean ± SD	114 ± 141	132 ± 173	0.06
	Range	1 - 1209	1 - 1433	
6 Minute Walk Distance (meters)	N	696	1069	
	Mean ± SD	363 ± 108	358 ± 106	0.44
	Range	31 - 896	0 - 744	
Euro Qol Index	N	726	1086	
	Mean ± SD	0.84 ± 0.13	0.84 ± 0.14	0.58
	Range	0.27 - 1.00	-0.04 – 1.00	
KCCQ Overall Summary Score	N	727	1087	

Characteristic	Measurement	ICD (N=731)	CRT-D (N=1089)	P-value
	Mean ± SD	75 ± 19	76 ± 18	0.43
	Range	10 - 100	17 - 100	
KCCQ Clinical Summary Score	N	727	1087	
	Mean ± SD	80 ± 18	80 ± 17	0.66
	Range	4 - 100	16 - 100	
KCCQ Quality of Life Score	N	727	1087	
	Mean ± SD	66 ± 25	67 ± 23	0.84
	Range	0 - 100	0 - 100	

* Statistically significant differences were found between systolic and diastolic blood pressure; these differences are not considered clinically meaningful.

Table 8: Baseline Echocardiographic Volumes (all patients randomized, N=1820) – Full Patient Population

Characteristic	Measurement	ICD (N=731)	CRT-D (N=1089)	P-value
Left ventricular end-systolic volume (ml)	N	724	1085	
	Mean ± SD	180 ± 52	176 ± 48	0.10
	Range	94 - 465	83 - 434	
Left ventricular end-diastolic volume (ml)	N	724	1085	
	Mean ± SD	251 ± 65	246 ± 60	0.10
	Range	134 - 601	134 - 564	

Table 9: Cardiac Medications (all patients randomized, N=1820) - Full Patient Population

Medication	ICD (N=731) [N (%)]	CRT-D (N=1089) [N (%)]	P-value
ACE (Angiotensin Converting Enzyme) / ARB (Angiotensin Receptor blockers)*	699 (95.6)	1039 (95.4)	0.83
Aldosterone Antagonist**	226 (30.9)	352 (32.3)	0.53
Amiodarone**	51 (7.0)	78 (7.2)	0.88
Beta Blockers*	681 (93.2)	1016 (93.3)	0.91
Class I antiarrhythmic agent**	3 (0.4)	12 (1.1)	0.11
Digitalis**	177 (24.2)	291 (26.7)	0.23
Diuretic*	533 (72.9)	824 (75.7)	0.19
Statin*	491 (67.2)	735 (67.5)	0.88

* Required Optimal Pharmacologic Therapy (OPT), unless contraindicated. Ischemic patients were required to have a statin prescribed.

** Adjunctive medications per medical discretion.

D. Safety and Effectiveness Results

1. Results: Safety Endpoint

The MADIT-CRT study assessed the safety of the Cognis, Livian, and Contak Renewal 3 RF HE CRT-D's by the system-related complication-free rate observed within the date of implant and three (3) months of follow-up. For the purposes of the safety analysis, three (3) month follow-up was defined as 91 days post-implant.

Data Analysis: All CRT-D patients (n=1079) who underwent an implant procedure were included in the primary safety analysis and were analyzed according to randomization assignment. A system-related complication that occurred within 91 days post-implant was included as an event in this analysis.

The hypothesis for the system-related complication-free rate was evaluated using the lower one-sided 95% confidence bound from the Kaplan-Meier estimated system-related complication-free rate. The rate reported was based on Kaplan-Meier estimates and the lower confidence bound was based on a log cumulative hazard transformation.

Patients who did not have a system-related complication within 91 days post-implant were censored at their date of death, withdrawal (if the patient did not agree to phone contact to collect event data), or at 92 days post-implant.

Results: A total of 1079 patients were randomized to CRT-D and underwent an implant procedure. 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 significantly greater than 70% and therefore passed the pre-specified safety endpoint. The value of 70% was selected based on previous studies designed to evaluate CRT-D devices. The Kaplan-Meier system-related complication-free graph and supporting data are shown below in Figure 1 and Table 10.

Figure 1: System-Related Complication-Free Rate Within 91 days -Full Patient Population

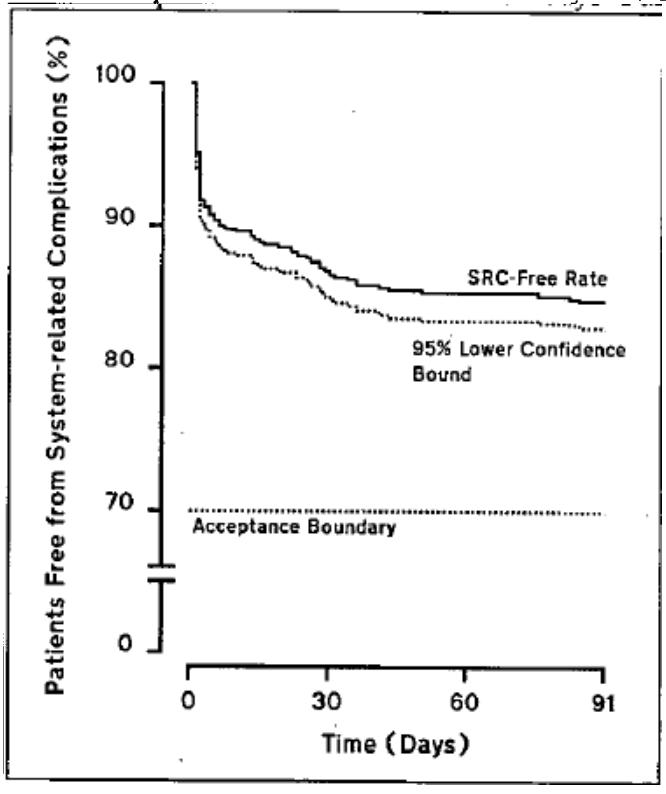


Table 10: System-Related Complication-Free Summary Data - Full Patient Population

Statistic	Days from Implant		
	0-30 Days	31-60 Days	61-91 Days
Number at Risk at Start of Interval	1079	933	917
Number of Patients in Interval	144	14	6
Cumulative Number of Patients	144	158	164
Number Censored in Interval	2	2	0
Cumulative Number Censored	2	4	4
Percent Free from Event	86.6%	85.3%	84.8%
95% Lower Confidence Bound	84.8%	83.5%	82.9%

There were 164 patients with system-related complications (214 total events). Of the 214 events, 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 TableTable 11. The sum of patients across categories does not equal the total number of unique patients because some patients had more than one (1) System-Related Complication.

Table 11: CRT System-Related Complication-Free Summary Data - Full Patient Population

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

Complication	Number of Events	Number of Patients	Complication Free Rate (%)	Lower One-Sided 95% Confidence Bound (%)
RV Lead	**15**	**15**	**98.6**	**97.9**
Dislodgment	8	8	99.3	98.7
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).

Results: Additional Safety Data

Cause of Death (All Patients)

Deaths for the full MADIT-CRT patient population are shown in Table 12 below. The most common causes of death in the study were pump failure (n=62, 38.8%) and non-cardiac causes (n=49, 30.6%), arrhythmic deaths (n=15, 9.4%), deaths from unknown causes (n=16, 10.0%).

Table 12: Cause of Death - Full Patient Population

Cause of Death Category	ICD (N=731)	CRT-D (N=1089)	Total (N=1820)
Cardiac: Pump failure	30 (44.1%)	32 (34.8%)	62 (38.8%)
Non-Cardiac	16 (23.5%)	33 (35.9%)	49 (30.6%)
Cardiac: Arrhythmic	8 (11.8%)	7 (7.6%)	15 (9.4%)
Unknown	7 (10.3%)	9 (9.8%)	16 (10%)
Cardiac: Ischemic	2 (2.9%)	6 (6.5%)	8 (5%)
Cardiac: Other procedure	2 (2.9%)	0 (0%)	2 (1.3%)
Cardiac: Other	1 (1.5%)	1 (1.1%)	2 (1.3%)
Not yet classified	2 (2.9%)	4 (4.3%)	6 (3.8%)
Total	68 (100%)	92 (100%)	160 (100%)

Cause of Death (Left Bundle Branch Block Patients Only)

The MADIT-CRT LBBB sub-population is the subset of patients enrolled in the MADIT-CRT study that have the same indications as those patients for which the new indication is being granted. The most common causes of death in the MADIT-CRT Left Bundle Branch Block (LBBB) sub-population were pump failure (n=41, 39.0%), non-cardiac causes (n=33, 31.4%), and arrhythmic deaths (n=10, 11.0%). Additionally, deaths from 12 patients (11.0%) were adjudicated and classified as unknown due to a lack of information from the investigational center. There were no statistically significant differences in the cause of death between treatment groups. The cause of death data are summarized below in Table 13.

Table 13: Cause of Death - LBBB Patient Sub-Population

Cause of Death Category	ICD (N=520)	CRT-D (N=761)	Total (N=1281)
Cardiac: Pump failure	22 (43.1%)	19 (35.2%)	41 (39%)
Non-Cardiac	16 (31.4%)	17 (31.5%)	33 (31.4%)
Cardiac: Arrhythmic	6 (11.8%)	4 (7.4%)	10 (9.5%)
Unknown	5 (9.8%)	7 (13%)	12 (11.4%)
Cardiac: Ischemic	1 (2%)	4 (7.4%)	5 (4.8%)
Cardiac: Other	1 (2%)	1 (1.9%)	2 (1.9%)
Not yet classified	0 (0%)	2 (3.7%)	2 (1.9%)
Total	51 (100%)	54 (100%)	105 (100%)

Of the 105 deaths in the LBBB patients, six (5.7%) were adjudicated as device-related (including procedure for device installation or maintenance) or possibly related to the device or procedure. Three occurred in the ICD group and three in the CRT-D group.

Of the 105 deaths in the LBBB patients, one occurred in a patient categorized as an intent (signed the consent and randomized, but never implanted) and five (4.8%) occurred prior to 91 days post implant. None of the deaths occurred within 24 hours of implant. Of the five patients that were implanted and then died within 91 days post-implant, one death occurred within 30 days of implant and four deaths occurred within 91 days post implant. The remaining 100 deaths occurred greater than 91 days post implant (95.2%).

Adverse Event Definitions

Investigators were responsible for providing a description of each reported adverse event including the suspected cause, corrective actions, and clinical outcome. All adverse events reported by centers were reviewed and classified as described below.

Adverse events were defined as any untoward clinical event, including events that were not related to the implanted system. Adverse events were ranked by severity. Events that were life-threatening, required an invasive intervention, resulted in hospitalization, permanent loss of device therapy, permanent disability, or death were defined as complications. Those events that were transient and reversible and resolved non-invasively without hospitalization were defined as observations. In Europe (per ISO 14155) reportable adverse events were classified as serious (equivalent to complications) or non-serious (equivalent to observations).

Patient-Related Adverse Events

In all patients, 5024 (81%) of the adverse events were related to patient condition rather than the implanted device, procedure or protocol. Of these, 2284 (45%) were non-cardiac related, 1711 (34%) were cardiac/non-heart failure related, and 1029 (20%) were cardiac/heart failure related.

In LBBB patients, 2161 (74%) of the adverse events were related to patient condition rather than the implanted device, procedure or protocol. Of these, 1091 (50%) were non-cardiac related, 762 (35%) were cardiac/non-heart failure related, and 308 (14%) were cardiac/heart failure related.

Device-Related Adverse Events

In all patients, 1276 (29.5%) of the adverse events were related to the device, implant procedure or protocol related testing. A summary of the device-related adverse events for the CRT-D treatment group is provided below in Table 14 for all patients and in Table 15 for LBBB patients only.

Table 14: Device-Related Adverse Events by System Component (Full Patient Population)

Component	Number Of Events (% of events)	Number Of Patients (% of patients with events)*
Pulse Generator Related	568 (44.5%)	409 (57%)
Procedure Related	353 (27.7%)	283 (39.4%)
Left Ventricular Lead Related	174 (13.6%)	149 (20.8%)
Right Atrial Lead Related	94 (7.4%)	81 (11.3%)
Right Ventricular Lead Related	81 (6.3%)	73 (10.2%)
Protocol-mandated Testing Related	6 (0.5%)	6 (0.8%)
Total Device/Procedure Adverse Events	1276 (100%)	718 (100%)

*Patients can be in more than one category so percent of patients with events does not equal 100%

Table15: Device-Related Adverse Events by System Component (LBBB Patient Sub-Population)

Component	Number Of Events (% of events)	Number Of Patients (% of patients with events)*
Pulse Generator Related	390 (43.0%)	286 (57.5%)
Procedure Related	262 (28.9%)	208 (41.9%)
Left Ventricular Lead Related	129 (14.2%)	106 (21.3%)
Right Atrial Lead Related	66 (7.3%)	57 (11.5%)
Right Ventricular Lead Related	54 (6.0%)	49 (9.9%)
Protocol-mandated Testing Related	5 (0.6%)	5 (1.0%)
Total Device/Procedure Adverse Events	906 (100%)	497 (100%)

* Patients can be in more than one category so percent of patients with events does not equal 100%.

Summary of All Adverse Events

A summary of the observations and complications for the CRT-D treatment group is provided below in Table 16 for all patients. In order to provide a broad yet concise summary of the adverse events, a summary of all observations and complications for the LBBB patients is not provided here. Infrequent events (defined as observations occurring in fewer than four patients) are summarized at the end of each section within the table.

Table 16: CRT-D Clinical Observation and Complication Summary (All Patients)

		Complications		Observations	
Adverse Event	**Total Number Of Events (Number of Patients)**	**% of Patients (N Patients)**	**N Events/ 100 Device Months (N Events)**	**% of Patients (N Patients)**	**N Events/ 100 Device Months (N Events)**
Total Adverse Events	**4323 (942)**	**65.2 (704)**	**5.39 (2014)**	**71.6 (773)**	**6.18 (2309)**
Pulse Generator (PG) Related Events					
Early elective replacement indicator	44 (43)	3.9 (42)	0.12 (43)	0.1 (1)	0.00 (1)
Elevated Defibrillation Thresholds	4 (4)	0.3 (3)	0.01 (3)	0.1 (1)	0.00 (1)
Erosion	6 (6)	0.6 (6)	0.02 (6)	0.0 (0)	0.00 (0)
Extracardiac stimulation – Left Ventricular Lead	127 (104)	0.2 (2)	0.01 (2)	9.5 (102)	0.33 (125)
Inappropriate tachyarrhythmia therapy	33 (27)	0.6 (7)	0.02 (7)	1.9 (21)	0.07 (26)
Infection (> 30 days post-implant)	12 (10)	0.6 (7)	0.02 (9)	0.3 (3)	0.01 (3)
Migration	4 (4)	0.1 (1)	0.00 (1)	0.3 (3)	0.01 (3)
Other – PG System - Patient	3 (3)	0.1 (1)	0.00 (1)	0.2 (2)	0.01 (2)
Oversensing – Right Atrial Lead	13 (11)	0.0 (0)	0.00 (0)	1.0 (11)	0.03 (13)
Oversensing – Right Ventricular Lead	5 (4)	0.1 (1)	0.00 (1)	0.3 (3)	0.01 (4)
Pacemaker-mediated tachycardia (PMT)	154 (116)	0.3 (3)	0.01 (3)	10.5 (113)	0.40 (151)
Programmer / Software error code	1 (1)	0.1 (1)	0.00 (1)	0.0 (0)	0.00 (0)
Threshold elevated/unable to capture – Left Ventricular Lead	32 (26)	0.2 (2)	0.01 (2)	2.3 (25)	0.08 (30)
Threshold elevated/unable to capture – Right Atrial Lead	4 (4)	0.0 (0)	0.00 (0)	0.4 (4)	0.01 (4)
Threshold elevated/unable to capture – Right Ventricular Lead	6 (6)	0.2 (2)	0.01 (2)	0.4 (4)	0.01 (4)
Unable to convert - Defibrillation	4 (4)	0.3 (3)	0.01 (3)	0.1 (1)	0.00 (1)
Undersensing - Defibrillation	1 (1)	0.1 (1)	0.00 (1)	0.0 (0)	0.00 (0)
Infrequent events include: Accelerated to AF (1), Cannot measure left ventricular lead impedance (1), Inappropriate AV delay (3), pulse generator system diagnosis - other (3), Psychological effect due to device therapy (1), Seroma - Pocket (> 30 days post-implant) (3), Undersensing – right atrial (1)					
Subtotal Pulse Generator Related Events	**466 (326)**	**7.5 (81)**	**0.23 (85)**	**25.4 (274)**	**1.02 (381)**
Right Atrial (RA) Lead Related Events					
Conductor coil fracture – RA	2 (2)	0.1 (1)	0.00 (1)	0.1 (1)	0.00 (1)
Impedance > 2000 ohms - RA	3 (3)	0.2 (2)	0.01 (2)	0.1 (1)	0.00 (1)

		Complications		Observations	
Adverse Event	Total Number Of Events (Number of Patients)	% of Patients (N Patients)	N Events/ 100 Device Months (N Events)	% of Patients (N Patients)	N Events/ 100 Device Months (N Events)
Insulation breach - RA	1 (1)	0.1 (1)	0.00 (1)	0.0 (0)	0.00 (0)
Lead dislodgment - RA	43 (40)	3.6 (39)	0.11 (42)	0.1 (1)	0.00 (1)
Oversensing – RA	9 (7)	0.1 (1)	0.00 (1)	0.6 (6)	0.02 (8)
Threshold elevated/unable to capture – RA	14 (14)	0.4 (4)	0.01 (4)	0.9 (10)	0.03 (10)
Subtotal RA Lead Related Events	**72 (62)**	**4.4 (47)**	**0.14 (51)**	**1.8 (19)**	**0.06 (21)**
Right Ventricular (RV) Lead Related Events					
Conductor coil fracture - RV	1 (1)	0.1 (1)	0.00 (1)	0.0 (0)	0.00 (0)
Impedance < 300 ohms - RV	1 (1)	0.1 (1)	0.00 (1)	0.0 (0)	0.00 (0)
Impedance > 2000 ohms - RV	1 (1)	0.0 (0)	0.00 (0)	0.1 (1)	0.00 (1)
Insulation breach - RV	1 (1)	0.1 (1)	0.00 (1)	0.0 (0)	0.00 (0)
Lead dislodgment - RV	10 (9)	0.8 (9)	0.03 (10)	0.0 (0)	0.00 (0)
Oversensing – RV	6 (6)	0.2 (2)	0.01 (2)	0.4 (4)	0.01 (4)
RV lead dislodgment	1 (1)	0.1 (1)	0.00 (1)	0.0 (0)	0.00 (0)
Threshold elevated/unable to capture – RV	10 (10)	0.4 (4)	0.01 (4)	0.6 (6)	0.02 (6)
Undersensing – RV	2 (2)	0.1 (1)	0.00 (1)	0.1 (1)	0.00 (1)
Subtotal RV Lead Related Events	**33 (32)**	**1.9 (20)**	**0.06 (21)**	**1.1 (12)**	**0.03 (12)**
Left Ventricular (LV) Lead Related Events					
Conductor coil fracture - LV	2 (2)	0.2 (2)	0.01 (2)	0.0 (0)	0.00 (0)
Extracardiac stimulation - LV	43 (40)	1.4 (15)	0.05 (17)	2.4 (26)	0.07 (26)
Impedance > 2000 ohms - LV	6 (6)	0.3 (3)	0.01 (3)	0.3 (3)	0.01 (3)
Insulation breach - LV	4 (4)	0.4 (4)	0.01 (4)	0.0 (0)	0.00 (0)
Lead dislodgment - LV	80 (68)	5.8 (63)	0.20 (73)	0.6 (7)	0.02 (7)
Threshold elevated/unable to capture – LV	24 (23)	0.6 (6)	0.02 (6)	1.6 (17)	0.05 (18)
Infrequent events include: Impedance < 300 ohms - LV (2), Oversensing - LV (1)					
Subtotal LV Lead Related Events	**162 (137)**	**8.2 (88)**	**0.28 (105)**	**5.0 (54)**	**0.15 (57)**
Defibrillator Lead Related Events					
Elevated DFT/ unable to convert	5 (5)	0.4 (4)	0.01 (4)	0.1 (1)	0.00 (1)
Inappropriate tachy therapy	5 (5)	0.2 (2)	0.01 (2)	0.3 (3)	0.01 (3)

		Complications		Observations	
Adverse Event	Total Number Of Events (Number of Patients)	% of Patients (N Patients)	N Events/ 100 Device Months (N Events)	% of Patients (N Patients)	N Events/ 100 Device Months (N Events)
Subtotal Defib Lead Related Events	**10 (10)**	**0.6 (6)**	**0.02 (6)**	**0.4 (4)**	**0.01 (4)**
Procedure Related Events					
AV block	11 (11)	0.6 (7)	0.02 (7)	0.4 (4)	0.01 (4)
Adverse reaction	23 (22)	0.6 (7)	0.02 (7)	1.4 (15)	0.04 (16)
Arterial perforation - Procedure	2 (2)	0.1 (1)	0.00 (1)	0.1 (1)	0.00 (1)
Coronary venous dissection	5 (5)	0.0 (0)	0.00 (0)	0.5 (5)	0.01 (5)
Coronary venous perforation without tamponade	5 (5)	0.2 (2)	0.01 (2)	0.3 (3)	0.01 (3)
Hematoma - Pocket (<=30 days post-implant)	39 (39)	1.4 (15)	0.04 (15)	2.2 (24)	0.06 (24)
Inadvertent Supraventricular Tachycardia	2 (2)	0.1 (1)	0.00 (1)	0.1 (1)	0.00 (1)
Inadvertent VT/VF	5 (5)	0.5 (5)	0.01 (5)	0.0 (0)	0.00 (0)
Myocardial perforation with tamponade	3 (3)	0.3 (3)	0.01 (3)	0.0 (0)	0.00 (0)
Other - Lead - Procedure	8 (8)	0.7 (8)	0.02 (8)	0.0 (0)	0.00 (0)
Other – PG system - Procedure	18 (17)	0.6 (6)	0.02 (6)	1.1 (12)	0.03 (12)
Pericardial effusion	9 (7)	0.4 (4)	0.01 (5)	0.3 (3)	0.01 (4)
Pleural effusion - Procedure	3 (3)	0.1 (1)	0.00 (1)	0.2 (2)	0.01 (2)
Pneumothorax - Procedure	21 (21)	1.5 (16)	0.04 (16)	0.5 (5)	0.01 (5)
Post-surgical infection (<= 30 days post-implant)	20 (17)	0.7 (8)	0.03 (11)	0.8 (9)	0.02 (9)
Post-surgical pocket hemorrhage	4 (4)	0.2 (2)	0.01 (2)	0.2 (2)	0.01 (2)
Post-surgical wound discomfort	29 (28)	0.0 (0)	0.00 (0)	2.6 (28)	0.08 (29)
Renal failure due to contrast media – Procedure	4 (4)	0.4 (4)	0.01 (4)	0.0 (0)	0.00 (0)
Seroma - Pocket (<=30 days post-implant)	4 (4)	0.1 (1)	0.00 (1)	0.3 (3)	0.01 (3)
Thromboembolic events	15 (15)	0.7 (8)	0.02 (8)	0.6 (7)	0.02 (7)
Venous occlusion	3 (3)	0.1 (1)	0.00 (1)	0.2 (2)	0.01 (2)
Infrequent events include: Chest pain (1), Hemorrhage (2), Vasovagal (2)					
Subtotal Procedure Related Events	**238 (187)**	**8.3 (90)**	**0.28 (104)**	**10.5 (113)**	**0.36 (134)**
Protocol Testing Related Events					
Chest pain	3 (3)	0.1 (1)	0.00 (1)	0.2 (2)	0.01 (2)

		Complications		Observations	
Adverse Event	Total Number Of Events (Number of Patients)	% of Patients (N Patients)	N Events/ 100 Device Months (N Events)	% of Patients (N Patients)	N Events/ 100 Device Months (N Events)
Fatigue	1 (1)	0.0 (0)	0.00 (0)	0.1 (1)	0.00 (1)
Integumentary	2 (2)	0.0 (0)	0.00 (0)	0.2 (2)	0.01 (2)
Subtotal Protocol Testing Related Events	**6 (6)**	**0.1 (1)**	**0.00 (1)**	**0.5 (5)**	**0.01 (5)**
Cardiovascular – Heart Failure (HF) Related Events					
Worsening heart failure	533 (287)	16.9 (184)	0.87 (325)	13.7 (149)	0.56 (208)
Subtotal Cardiovascular - HF Related Events	**533 (287)**	**16.9 (184)**	**0.87 (325)**	**13.7 (149)**	**0.56 (208)**
Cardiovascular - Non-Heart Failure (Non-HF) Related Events					
Bleeding	12 (12)	0.8 (9)	0.02 (9)	0.3 (3)	0.01 (3)
Bradyarrhythmias	24 (24)	0.5 (5)	0.01 (5)	1.7 (19)	0.05 (19)
Cardiogenic shock	1 (1)	0.1 (1)	0.00 (1)	0.0 (0)	0.00 (0)
Chest pain	233 (162)	8.2 (89)	0.31 (116)	8.4 (91)	0.31 (117)
Dizziness	67 (64)	1.2 (13)	0.03 (13)	4.9 (53)	0.14 (54)
Dyspnea	49 (45)	1.2 (13)	0.03 (13)	3.2 (35)	0.10 (36)
Fatigue	25 (25)	0.1 (1)	0.00 (1)	2.2 (24)	0.06 (24)
Hypo/hypertension	105 (88)	2.1 (23)	0.07 (27)	6.2 (67)	0.21 (78)
Myocardial infarction	37 (31)	2.8 (31)	0.10 (37)	0.0 (0)	0.00 (0)
Other - Patient condition - Cardiovascular	92 (85)	4.0 (44)	0.12 (46)	3.9 (42)	0.12 (46)
Palpitations	37 (28)	0.2 (2)	0.01 (2)	2.4 (26)	0.09 (35)
Related to Vasculature	2 (2)	0.2 (2)	0.01 (2)	0.0 (0)	0.00 (0)
Supraventricular tachyarrhythmias	238 (173)	6.9 (75)	0.26 (96)	10.8 (118)	0.38 (142)
Syncope	43 (36)	1.6 (17)	0.05 (19)	1.8 (20)	0.06 (24)
Vascular	102 (82)	6.1 (66)	0.22 (82)	1.7 (19)	0.05 (20)
Ventricular tachyarrhythmias	126 (91)	5.6 (61)	0.22 (81)	3.7 (40)	0.12 (45)
Subtotal Cardiovascular - Non-HF Related Events	**1193 (580)**	**30.6 (333)**	**1.47 (550)**	**36.4 (396)**	**1.72 (643)**
Subtotal Non-cardiovascular Related Events	**1610 (635)**	**38.0 (414)**	**2.05 (766)**	**39.2 (427)**	**2.26 (844)**

2. Results: Primary Effectiveness Endpoint

The MADIT-CRT study assessed the effectiveness of CRT-D by the relative reduction of the risk of the combined endpoint of all-cause mortality or heart failure event, whichever occurred first, when compared to ICD.

Data Analysis: Statistical tests of the difference in the primary effectiveness endpoint (rate of combined all-cause mortality or heart failure event, whichever occurred first) between the randomized CRT-D and ICD groups were performed. The primary effectiveness analysis was based on comparing the Kaplan-Meier life-table event-free survival time graphs for the CRT-D and ICD groups. The stratified log-rank test (stratified by clinical center and ischemic status) was used to evaluate statistical significance, adjusting for the group-sequential stopping rule of the study. The hazard ratio for CRT-D relative to ICD, based on proportional hazards modeling, was also estimated, along with the corresponding 95% confidence limits.

All analyses were carried out according to the intention-to-treat principle and include data occurring on or before December 31, 2009. Patients who did not have a primary endpoint by December 31, 2009, were censored at either their date of withdrawal (if the patient did not agree to phone contact to collect event data) or last visit.

Results: In the full patient population, 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 $p<0.001$. However, post-hoc subgroup analyses revealed that there was no evidence of benefit in the non-LBBB patient sub-population and that the results were driven by the LBBB patient sub-population, which comprised 70% of the total cohort. The adjusted hazard ratio was 0.61, with 95% confidence interval (0.50 to 0.75), and $p<0.001$.

In the LBBB patient sub-population, CRT-D was associated with a reduction in the relative risk of death or heart failure event by 57% as compared to ICD. 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 2. A table summarizing the data supporting the Kaplan-Meier curves is shown below in Table 17. The components of the primary effectiveness endpoint are shown below in Table 18.

Figure 2: K-M Curves of Time to All-Cause Mortality or HF Event (LBBB Patients Only)
All LBBB patients, N=1281

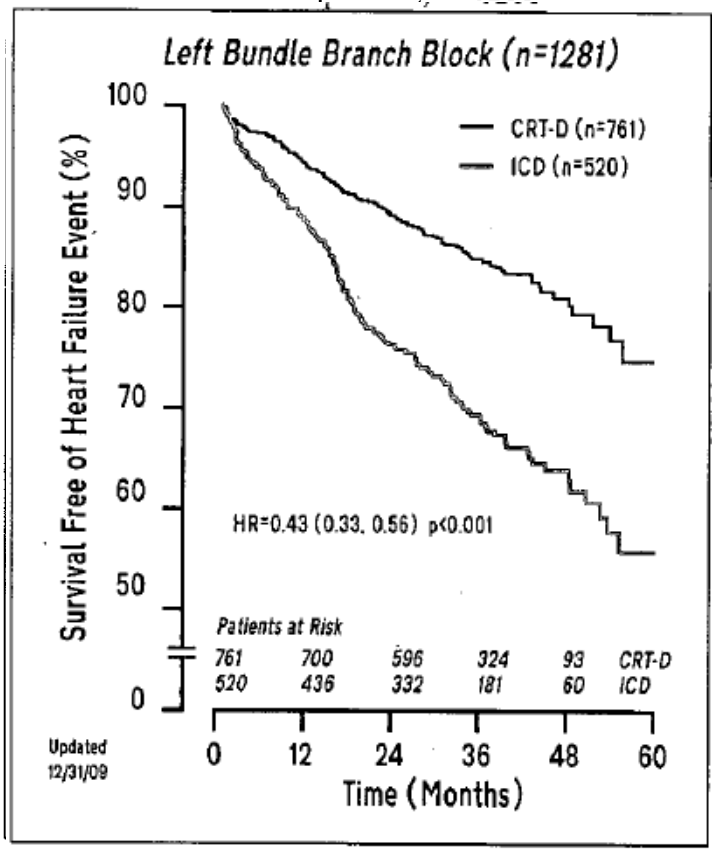


Table 17: Summary of K-M All-Cause Mortality or HF Events (LBBB Patients Only)
All LBBB patients, N=1281

	ICD					CRT-D				
Months	**0-12**	**12-24**	**24-36**	**36-48**	**48-60**	**0-12**	**12-24**	**24-36**	**36-48**	**48-60**
N Patients at Start of Interval	520	436	332	181	60	761	700	596	324	93
N Patients with Endpoint Events	63	58	26	11	4	47	37	22	11	3
N Patients with Endpoint Events (cumulative)	63	121	147	158	162	47	84	106	117	120
N Patients Censored	21	46	125	110	56	14	67	250	220	90
N Patients Censored (cumulative)	21	67	192	302	358	14	81	331	551	641
Percent Free from Event	87.6%	75.8%	68.2%	61.8%	55.8%	93.8%	88.7%	84.5%	79.4%	74.7%
95% Lower Confidence Bound	84.4%	71.8%	63.6%	56.0%	47.9%	91.8%	86.2%	81.5%	74.9%	67.4%

Table 18: Primary Effectiveness Endpoint Components (LBBB Patients Only)
All LBBB patients, N=1281

Item	**Number of Patients (% of All Patients in Treatment Group)**			
	ICD (N=520)	**CRT-D (N=761)**	**Hazard Ratio (95% Confidence Interval)**	**P-value**
Patients with Primary Endpoint Event	162 (31%)	120 (16%)	0.43 (0.33, 0.56)	<.001
Patients with All-Cause Mortality at Any Time*	51 (10%)	54 (7%)	0.65 (0.42, 1.00)	0.044
Patients with HF Event	144 (28%)	89 (12%)	0.37 (0.28, 0.50)	<.001
Inpatient HF Event	116 (22%)	76 (10%)	---	---
Outpatient HF Event	28 (5%)	13 (2%)	---	---

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

Kaplan-Meier curves for the primary endpoint and its components are presented in Figures 3 through 5 below.

Figure 3: Kaplan-Meier Curves for Primary Endpoint

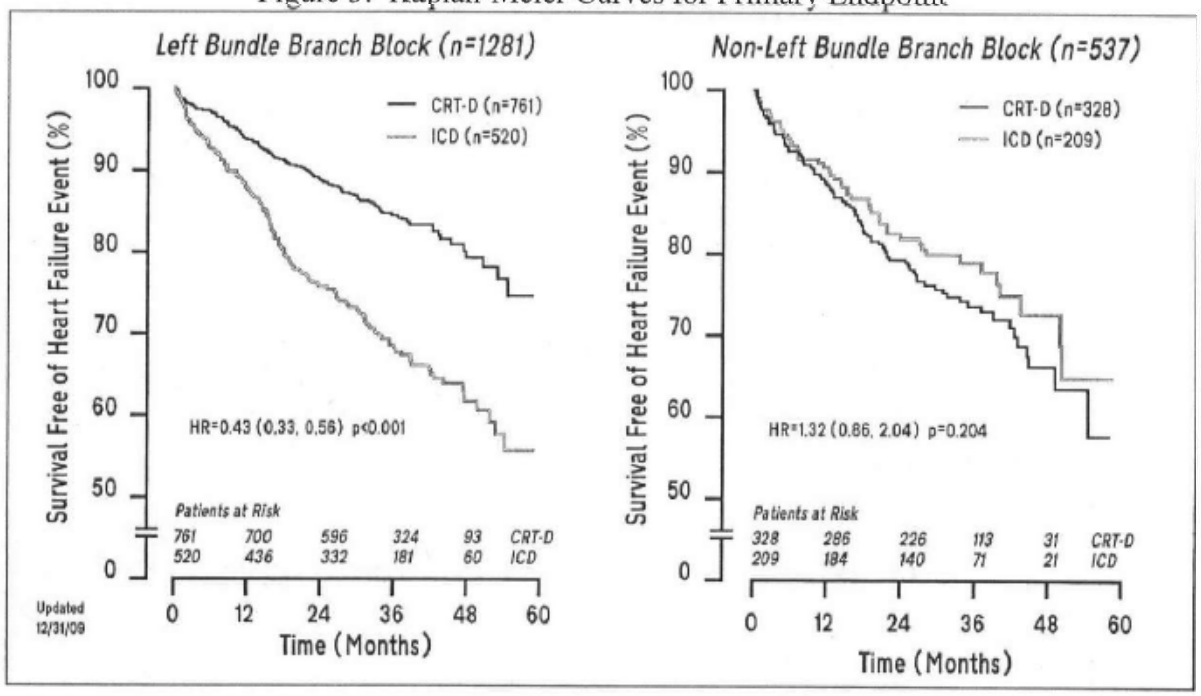


Figure 4: Kaplan-Meier Curves for First Heart Failure Event

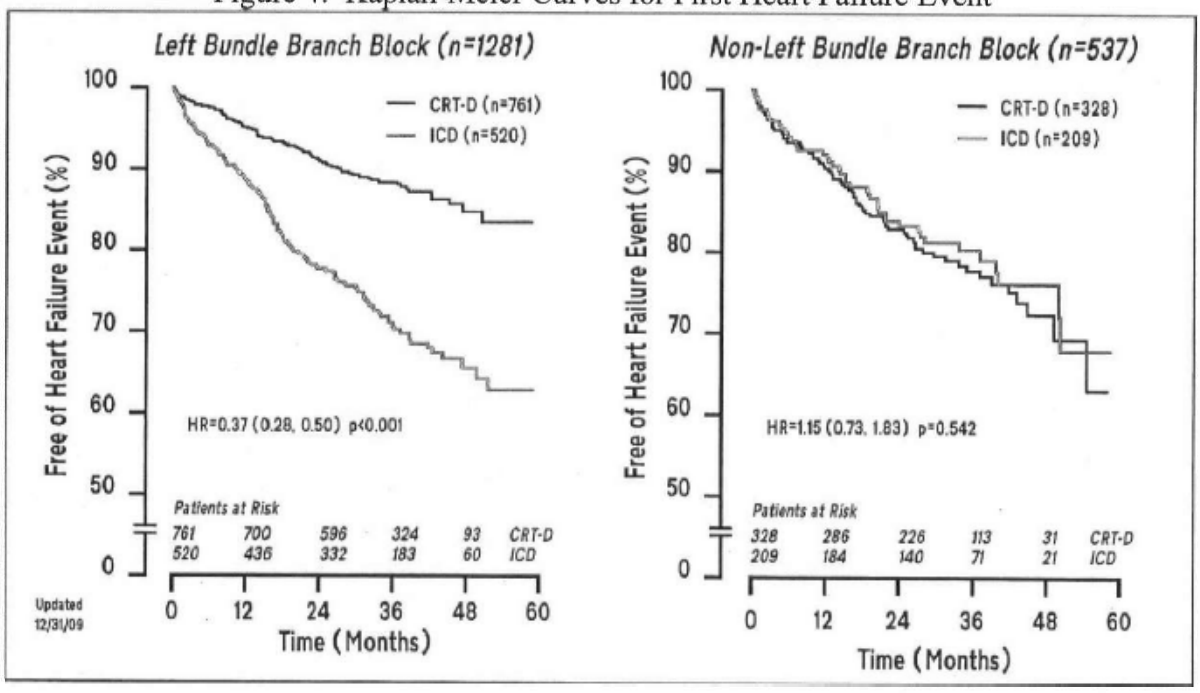
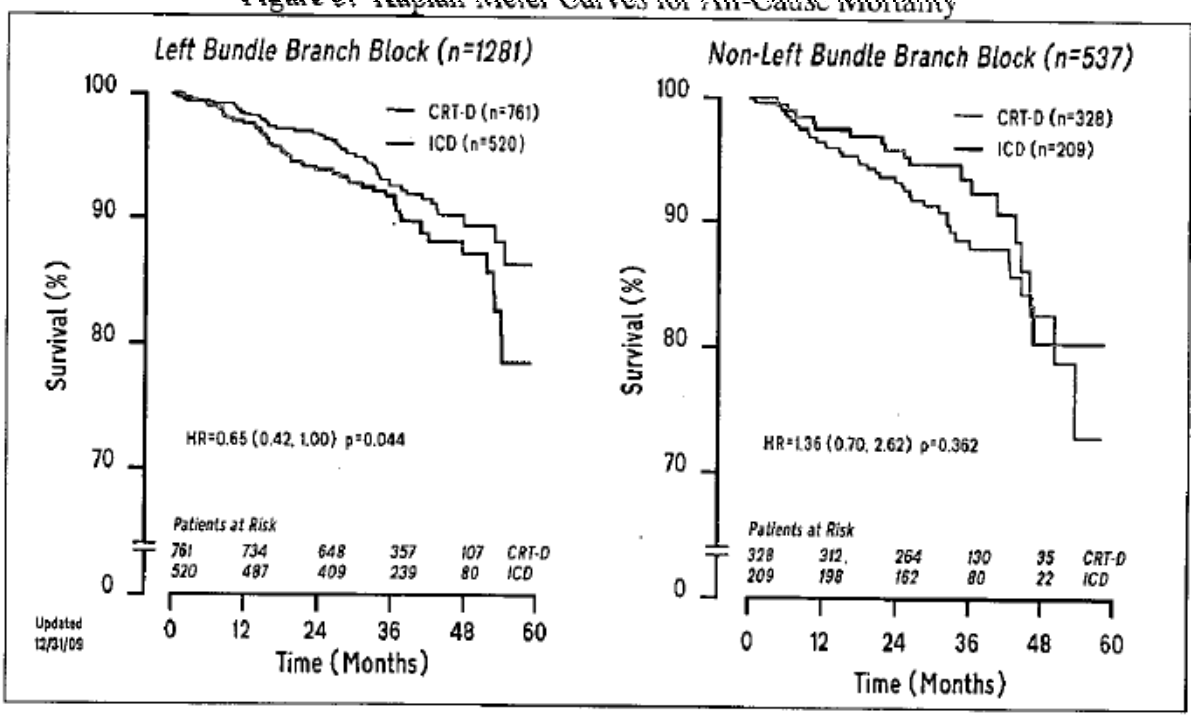


Figure 5: Kaplan-Meier Curves for All-Cause Mortality



Results: Secondary Endpoint

The MADIT-CRT study also evaluated the effects of CRT-D, relative to ICD, on the recurrence of heart failure events over the full study period.

Data Analysis: The analysis was based on the intention-to-treat principle. The number of heart failure events occurring within the period of active follow-up of each patient was analyzed to determine whether the average rate within the CRT-D group differed from that in the ICD group. An Andersen-Gill regression analysis was performed to assess the benefit of CRT-D on recurrent heart failure events. In the Andersen-Gill regression analysis, patients were censored at their date of death, withdrawal (if patient did not agree to phone contact to collect event data) or last visit.

Results: In the full patient population, CRT-D was associated with a statistically significant reduction in the risk of recurrent heart failure events when compared to ICD. However, there was no evidence of benefit in the non-LBBB patient sub-population, and the results were driven by the LBBB patient sub-population.

In the LBBB patient sub-population, CRT-D was associated with a reduction in the risk of recurrent heart failure events by 43% when compared to ICD. A summary of the number of all heart failure events experienced for LBBB patients according to treatment group is presented below in Table 19.

Table 19: Number of Heart Failure Events by Treatment Arm (LBBB Patients Only)
All LBBB patients, N=1281

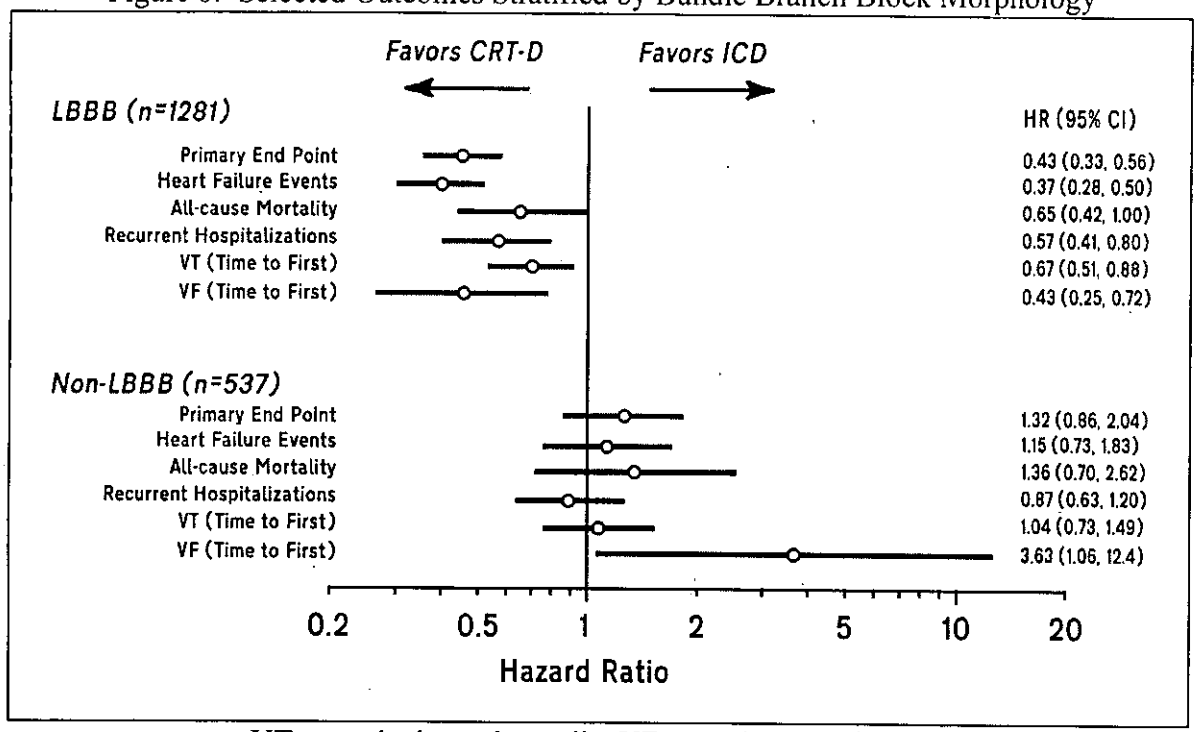
Number of HF Events	Number of Patients (% of All Patients in Treatment Group)	
	ICD (N=520)	CRT-D (N=761)
0	376 (72.3%)	672 (88.3%)
1	89 (17.1%)	51 (6.7%)
2+	55 (10.6%)	38 (5.0%)

Rates of heart failure events can be presented two ways, 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 53 HF events for every 100 patients and 18.5 HF events for every 100 patient-years of follow-up, whereas patients randomized to CRT-D experienced 22 HF events for every 100 patients and 7.5 HF events for every 100 patient-years of follow-up.

3. Results: Subgroup Analyses

A subgroup analysis based on pre-specified clinical baseline characteristics revealed statistically significant interactions with sex and QRS width such that female patients and those patients with QRS $\geq$ 150 ms derived the greatest benefit from CRT-D. During a post hoc investigation of benefit in female patients, a disparity in the prevalence of left bundle branch block (LBBB) morphology between women and men was discovered in which women were more likely than men to have LBBB. The study results were subsequently examined by bundle branch morphology in a post-hoc analysis. When compared to the non-LBBB cohort, LBBB was associated with substantially greater improvement across the primary endpoint and its components, the secondary endpoint, and some tertiary endpoints as shown in Figure 6 below.

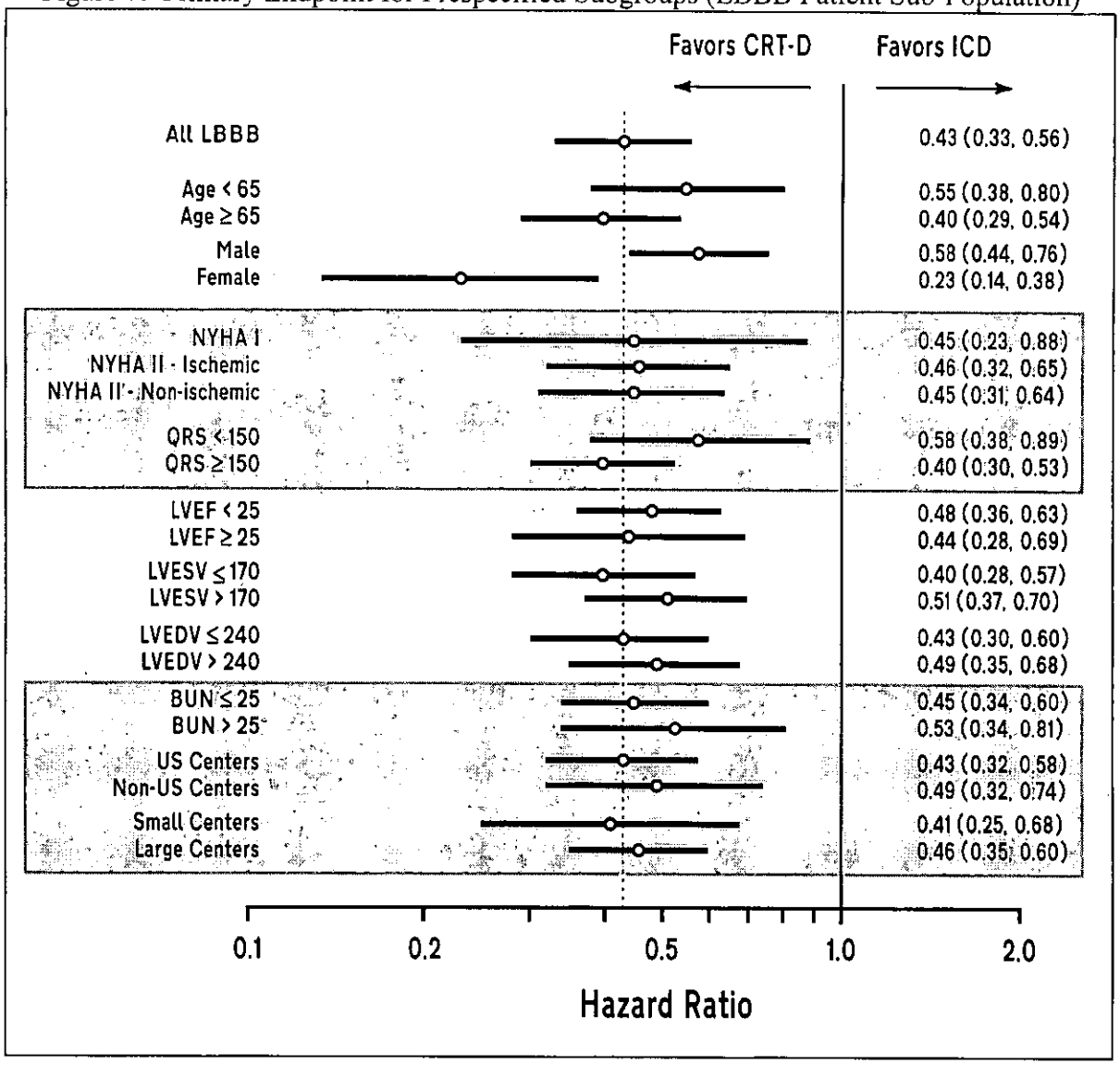
Figure 6: Selected Outcomes Stratified by Bundle Branch Block Morphology



VT=ventricular tachycardia, VF=ventricular fibrillation

An exploratory analysis restricted to the LBBB patient population revisited the primary endpoint of the prespecified covariates. As shown in Figure 7, each patient population demonstrated consistent improvement with CRT-D.

Figure 7: Primary Endpoint for Prespecified Subgroups (LBBB Patient Sub-Population)



Multivariate Analysis (LBBB Patients Only)

Multivariate analyses were performed in order to determine which baseline clinical variables in addition to treatment were significantly associated with outcomes. The outcomes examined included the primary endpoint and its components and the secondary endpoint. For the primary endpoint and its components, a multivariate Cox proportional hazards model was constructed. For the secondary endpoint, an Andersen-Gill model was used.

CRT-D as a treatment was consistently associated with significantly improved outcomes. In general, covariates associated with worsened baseline condition (e.g. six minute walk distance, NYHA Class and impaired renal function) were also associated with the greater risk of an event. Heart failure medications that improve outcomes, such as angiotensin converting enzymes (ACE), angiotension receptor blockers (ARB), and beta blockers at the target dose were also associated with better prognosis. However, the use of loop diuretics

and amiodarone were associated with poorer outcomes, possibly linked to their use to treat volume overload and atrial fibrillation, respectively. For the secondary endpoint, the most powerful predictor of recurrent heart failure events included prior events.

Two (2) variables were associated with significant interactions: sex and systolic blood pressure. Women were significantly more likely to derive benefit from CRT-D than men while CRT-D conferred greater benefit to patients with lower systolic blood pressure.

Study Conclusion of Safety and Effectiveness

In the MADIT-CRT study, the safety and primary effectiveness endpoints were met for the full population studied. However, there was no evidence of benefit in the non-LBBB patient sub-population as the results were predominately driven by the LBBB patient sub-population. A retrospective analysis by bundle branch morphology revealed that CRT-D conferred the greatest benefit in patients with left bundle branch block.

In patients with LBBB, the CRT-D system-related complication-free rate between implant and three months of follow-up was 83.4%; this result was greater than the pre-specified boundary of 70%. CRT-D, when compared to ICD, also reduced the relative risk of the following:

- Combined endpoint of all-cause mortality or heart failure event by 57%
- Heart failure events alone by 63%
- All-cause mortality by 35%
- Recurrent heart failure events by 43%

Therefore, the LBBB sub-population from the MADIT-CRT study demonstrated the safety and effectiveness of Boston Scientific CRT-D devices in patients that have LBBB with QRS $\geq$ 130 ms, EF $\leq$ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure.

Tertiary Endpoints (LBBB Patients Only)

There were ten (10) pre-specified tertiary endpoints for this study. For each endpoint, the objective, analysis methods, results and conclusions are provided. Core labs were utilized to reduce variability as well as evaluate and classify tertiary endpoint data specifically related to electrogram analysis and device interrogation, echocardiogram, quality of life (QOL), brain natriuretic peptide (BNP), and Holter. These analyses are exploratory, and the results should be considered suggestive and not definitive. Future studies would be needed to confirm these results.

All-Cause Mortality

Objective: Evaluate the effects of CRT-D on all-cause mortality.

Endpoint Results: Death occurred in 7.1% (n=54) of the patients in the CRT-D group and 9.8% (n=51) of the patients in the ICD group. The hazard ratio for all-cause mortality was

0.65. These results indicated an association with CRT-D and a reduction in all-cause mortality rate.

All-Cause Mortality Conclusion: Within the MADIT-CRT LBBB sub-population, CRT-D was associated with a reduction of 35% in the risk of all-cause mortality.

Appropriate Defibrillator Therapy

Objective: Evaluate the effects of CRT-D on appropriate defibrillator therapy for ventricular tachycardia (VT) and ventricular fibrillation (VF).

Endpoint Results: Rates of tachyarrhythmias are calculated by the total number of events (VT, VF and VT or VF) in the randomized group divided by the total follow-up years in the randomized group. Patients randomized to ICD experienced 49.6 VT events, 11.6 VF events, and 61.2 VT or VF events per 100 patient-years of follow-up; whereas patients randomized to CRT-D experienced 31.6 VT events, 2.0 VF events, and 33.7 VT or VF events per 100 patient-years of follow-up respectively. From the time-to-first event model, CRT-D was associated with reductions in VT, VF, or combination of VT and VF of 33%, 57%, and 34% respectively. The results from the recurrent event model were consistent in magnitude with the first event model.

Appropriate Therapy Conclusion: When compared to ICD, CRT-D with the MADIT-CRT LBBB sub-population was associated with a reduction in the risk of ventricular tachyarrhythmias using a time to first event model. When using a recurrent events model, CRT-D was associated with a reduction in VT, VF, and combined VT and VF.

Echocardiographic Structure and Function

Objective: Evaluate the effects of CRT-D, relative to ICD, on the changes from baseline to one (1) year in echo-determined left ventricular internal volume at end-systole (LVESV) and at end-diastole (LVEDV). The changes from baseline to one (1) year in left ventricular ejection fraction (LVEF) were also evaluated.

Endpoint Results: At 12 months, the mean change in LVESV in the CRT-D group from baseline was a reduction of 62 ml, as compared to 19 ml in the ICD group. Similarly, the mean change in LVEDV at 12 months in the CRT-D group was a reduction of 57 ml, as compared to 15 ml in the ICD group. Additionally, the mean change at 12 months in LVEF in the CRT-D group was an improvement of 12%, as compared to 3% in the ICD group.

Echocardiographic Structure and Function Conclusion: CRT-D was associated with a reduction in left ventricular volumes and an improvement in left ventricular ejection fraction as compared to ICD. Note, however, that these results should be interpreted with extreme caution, as CRT was not turned off but remained on during the echocardiographic measurements and might have influenced the results.

New York Heart Association Class

Objective: Evaluate the effects of CRT-D, relative to ICD, on the changes from baseline to one (1) year in NYHA functional class. It was hypothesized that, at one (1) year, the proportion of patients with symptomatic improvement would be greater with CRT-D when compared to ICD, after adjusting for any differences in baseline values.

Endpoint Results: Overall, there were associations between treatment group and change in NYHA based on the five (5) degrees of freedom test. For NYHA class I patients at baseline, there was not an association between NYHA functional class and treatment group. For NYHA class II patients at baseline, the results demonstrated changes for both the ischemic and non-ischemic subgroups. Combining the same and improved groups together also demonstrated an association between treatment group and change in NYHA class at 12 months, confirming analysis of all three (3) change groups (same, worsened, improved from the baseline functional class).

New York Heart Association Class Conclusion: There was no evidence of an association between treatment group and improvement in NYHA at 12 months for the subgroup of patients who were NYHA I at baseline. However, there were associations between treatment group and improvement in NYHA class at 12 months in NYHA II patients, both overall and within the ischemic/non-ischemic patients. Thus, in the MADIT-CRT LBBB sub-population, the Cognis, Livian, and Contak Renewal 3 RF HE CRT-D's lowered NYHA functional class in the NYHA class II patients.

Quality of Life

Quality of life was assessed with two (2) tools, the EQ-5D Questionnaire and the Kansas City Cardiomyopathy Questionnaire (KCCQ). EQ-5D, formerly known as EuroQol, is a generic assessment tool used to describe and value patients' health related to mobility, self-care, usual activity, pain and discomfort, anxiety and depression, and overall health state while KCCQ is specific to heart failure and monitors physical function, symptoms (frequency, severity, and recent change), social function, self-efficacy and knowledge, and quality of life. The KCCQ analysis presented here only focuses on the quality of life parameter.

Objective: Evaluate the effects of CRT-D, relative to ICD, on the changes in quality of life at 12 months and within the full study period. It was hypothesized that the assessed quality of life in the CRT-D group would, on average, exceed that in the ICD group.

Endpoint Results – EQ-5D: The range of the EQ-5D tool was from 0.0 (death) to 1.0 ("perfect health"), with 1.0 reflecting the best health state. The summary score was 0.04 in the CRT-D group and 0.02 in the ICD group. The differences in EQ-5D summary utility score at 12 months and the last follow-up visit for each treatment group were negligible.

Endpoint Results – KCCQ: The mean change in the KCCQ quality of life score at 12 months was 14.7 for the CRT-D group and 12.6 for the ICD group. The mean change in

the KCCQ clinical summary score at the last observed measurement was 14.8 for the CRT-D group and 10.6 for the ICD group.

Quality of Life Conclusion: Within the MADIT-CRT LBBB sub-population, improvements in quality of life as measured by the KCCQ and ED-5D assessment tools were observed with CRT-D when compared to ICD. However, the magnitude of these changes was modest, given that the patient population selected had relatively good quality of life scores at study entry.

Mitral Regurgitation

Objective: Evaluate the degree of mitral regurgitation (MR) by echocardiographic/ Doppler technique between the treatment groups at 12 months.

Endpoint Results: The distribution of the change in mitral regurgitation severity at 12 months was similar in both treatment groups (0.15 in the CRT-D group and 0.03 in the ICD group), with the majority of all patients having no change. The difference between the groups was negligible.

Mitral Regurgitation Conclusion: Although there was a difference between treatment groups in the change in mitral regurgitation severity from baseline to 12 months in the MADIT-CRT LBBB sub-population, this change was negligible.

Functional Capacity

Objective: Evaluate whether functional capacity (as measured by distance achieved during a six (6) minute hall walk) at the 12-month follow-up was greater in the CRT-D group than in the ICD group.

Endpoint Results: The mean change in the distance walked at 12 months was 14 meters for the CRT-D group and 10 meters for the ICD group.

Functional Capacity Conclusion: There was no evidence of an association between treatment group and change in functional capacity at 12 months in the MADIT-CRT LBBB sub-population.

Association of Brain Natriuretic Peptide and Outcome

Objective: Evaluate the association between the level of brain natriuretic peptide (BNP) at baseline and outcome (all-cause mortality or heart failure event) in patients randomized to CRT-D.

Endpoint Results: The hazard ratio for the association of baseline log10 BNP and outcome was 2.44, indicating that patients with a one (1) unit higher baseline log10 BNP were at almost a 2.5-fold increased risk of having a heart failure event or death. The results support an association between higher values of log10 baseline BNP and the risk of having

a heart failure event or death in US patients in the CRT-D group (n=724 patients with evaluable data). Centers located outside of the US (OUS) did not participate in this sub study due to the logistical difficulty with shipment of blood.

Association of Brain Natriuretic Peptide and Outcome Conclusion: In the CRT-D group there was an association between higher values of baseline log10 BNP and the risk of having a heart failure event or death. Thus, in the MADIT-CRT LBBB sub-population, there was an association in baseline BNP and outcome with CRT-D.

Brain Natriuretic Peptide

Objective: At US sites, Evaluate whether the level of brain natriuretic peptide (BNP) at the 12-month follow-up visit was lower in the CRT-D group than in the ICD group.

Endpoint Results: The mean change in BNP was -32 for the CRT-D group and +6 in the ICD group.

Brain Natriuretic Peptide Conclusion: The CRT-D group had a larger reduction in BNP than the ICD group. Thus, in the MADIT-CRT LBBB sub-population, CRT-D was associated with lower BNP at 12 months.

Holter Recorded Non-invasive Electrocardiographic Parameters and Hemodynamic Benefit

Objective: Evaluate whether Holter-recorded non-invasive electrocardiographic parameters can identify patients with increased hemodynamic benefit in CRT responders and non-responders.

Endpoint Results: In patients with a reduction of 20 ml or more in left ventricular end diastolic volume (LVEDV) at 12 months, their baseline QRS duration was associated with a hemodynamic benefit. Every ten (10) millisecond increase in baseline QRS duration corresponded to a 34% greater odds of having a reduction of 20 ml or more in LVEDV which was the pre-specified definition of a CRT responder.

Holter Conclusion: In the MADIT-CRT LBBB sub-population, baseline QRS duration was a predictor of CRT-D benefit (defined as a reduction in LVEDV of 20 ml or more).

Risk/Benefit Analysis

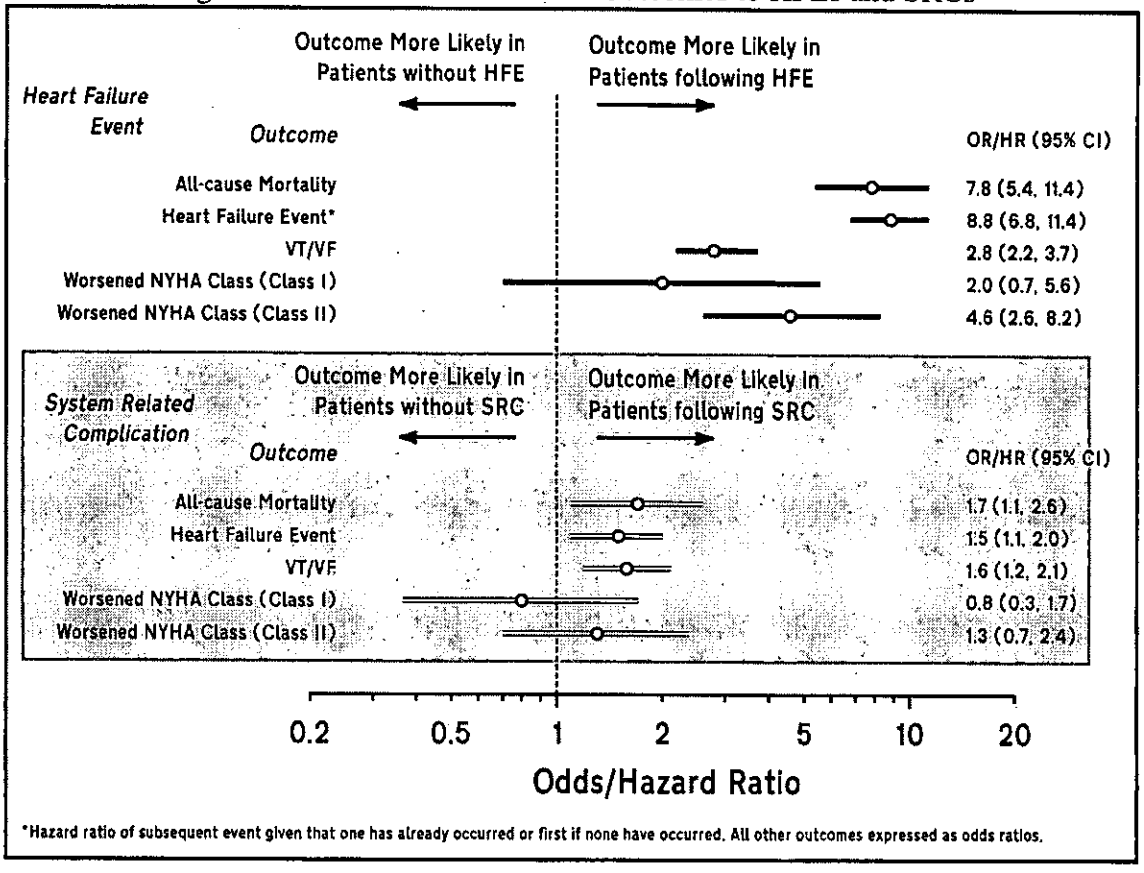
In the MADIT-CRT trial, the incremental risk associated with implantation of a CRT-D system is outweighed by the observed benefit in decreasing the progression of heart failure status. The incremental risk is reflected in the incidence of system- related complications (SRCs) while the benefit is shown in the relative reduction in heart failure events (HFEs). Although the absolute rates of HFEs and SRCs over time were similar, the long-term sequelae associated with an HFE could have a greater impact on a patient's clinical status than the long-term sequelae 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. 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 (2) 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 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 8 below.

Figure 8: 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, 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.

Gender Analysis

In MADIT-CRT, both men and women demonstrated significant improvement with CRT-D as compared to ICD. A significant interaction by treatment and sex was detected such that females received greater benefit. MADIT-CRT was not designed to analyze outcomes by sex; consequently these results should be considered to be exploratory. The following data were analyzed for all patients and for the LBBB patients: baseline demographics, safety endpoint, primary effectiveness endpoint, and the secondary effectiveness endpoint.

Baseline Demographics

As delineated below in Table 20, a univariate analysis revealed multiple differences in baseline characteristics between males and females that were statistically significant ($p<0.05$).

Covariates with clinically meaningful differences that may be associated with enhanced benefit in females with CRT-D include: NYHA Class II, non-ischemic etiology, and the presence of LBBB.

Table 20: Baseline Demographics by Sex (All Patients)

Characteristic	Measurement	Female (N=453)	Male (N=1367)	P-value
Basic Demographics				
Race [N (%)]	White	389 (85.9)	1249 (92.1)	<0.001
	Black/African American	56 (12.4)	87 (6.4)	
	Other	8 (1.8)	20 (1.5)	
Cardiac History				
NYHA Class/Ischemic [N (%)]	Class I Ischemic	23 (5.1)	242 (17.7)	<0.001
	Class II Ischemic	102 (22.5)	632 (46.2)	
	Class II Non-Ischemic	328 (72.4)	493 (36.1)	
Number of CHF Hospitalizations Prior to Enrollment [N (%)]	None	249 (56.5)	858 (63.9)	0.003

Characteristic	Measurement	Female (N=453)	Male (N=1367)	P-value
	1 – 2	176 (39.9)	420 (31.3)	
	3 or more	16 (3.6)	65 (4.8)	
Cardiac Risk Factors				
Atrial fibrillation > 1 month before enrollment	N (%)	32 (7.1)	176 (12.9)	<0.001
Cigarette Smoking	N (%)	39 (8.8)	175 (13.0)	0.02
Coronary-bypass surgery	N (%)	52 (11.5)	473 (34.6)	<0.001
Cardiac Findings at Enrollment				
Diastolic Blood Pressure (mm Hg)	N	448	1345	
	Mean ± SD	71 ± 11	72 ± 10	0.04
	Range	37 – 107	40 - 110	
BUN >= 26 mg/dL	N (%)	82 (18.2)	345 (25.5)	0.002
Creatinine (mg/dl)	N	451	1357	
	Mean ± SD	1.0 ± 0.3	1.2 ± 0.4	<0.001
	Range	0.4 - 2.2	0.5 - 7.2	
Conduction	LBBB [N (%)]	394 (87.0)	887 (65.0)	<0.001
	RBBB [N (%)]	18 (4.0)	210 (15.4)	<0.001
	IVCD [N (%)]	40 (8.8)	253 (18.5)	<0.001
LVEF (%)	N	453	1367	
	Mean ± SD	23 ± 5	24 ± 5	0.04
	Range	7 – 30	6 - 35	
6 Minute Walk Distance (meters)	N	434	1331	
	Mean ± SD	328 ± 107	371 ± 105	<0.001
	Range	31 – 686	0 - 896	
Euro Qol Index	N	451	1361	
	Mean ± SD	0.82 ± 0.13	0.85 ± 0.14	<0.001
	Range	0.20 - 1.00	-0.04 - 1.00	
KCCQ Overall Summary Score	N	452	1362	
	Mean ± SD	72 ± 19	77 ± 18	<0.001
	Range	17 – 100	10 - 100	
KCCQ Clinical Summary Score	N	452	1362	

Characteristic	Measurement	Female (N=453)	Male (N=1367)	P-value
	Mean ± SD	76 ± 18	81 ± 17	<0.001
	Range	11 – 100	4 - 100	
KCCQ Quality of Life Score	N	452	1362	
	Mean ± SD	61 ± 24	68 ± 23	<0.001
	Range	0 – 100	0 - 100	
Echocardiographic or Doppler findings				
Left ventricular end-stystolic volume (ml)	N	451	1358	
	Mean ± SD	156 ± 38	184 ± 51	<0.001
	Range	89 – 371	83 - 465	
Left ventricular end-diastolic volume (ml)	N	451	1358	
	Mean ± SD	220 ± 47	258 ± 63	<0.001
	Range	134 – 448	145 - 601	
Medications				
Aldosterone Antagonist	[N (%)]	165 (36.4)	413 (30.2)	0.01
Amiodarone	[N (%)]	12 (2.6)	117 (8.6)	<0.001
Beta Blockers	[N (%)]	436 (96.2)	1261 (92.2)	0.003
Digitalis	[N (%)]	165 (36.4)	303 (22.2)	<0.001
Diuretic	[N (%)]	331 (73.1)	897 (65.6)	0.003
Statin	[N (%)]	236 (52.1)	990 (72.4)	<0.001

The study results were subsequently examined by bundle branch morphology in a post-hoc analysis. Even when LBBB is taken into account, CRT-D still confers a substantially greater benefit in women when compared to men. Therefore, Table 21 presents a comparison of the demographics for males and females in the subgroup of patients with LBBB.

Table 21: Baseline Demographics by Sex (LBBB Patients Only)

Characteristic	Measurement	Female (N=394)	Male (N=887)	P-value
Basic Demographics				
Race [N (%)]	White	344 (87.3)	823 (93.5)	0.001
	Black/African American	44 (11.2)	49 (5.6)	
	Other	6 (1.5)	8 (0.9)	

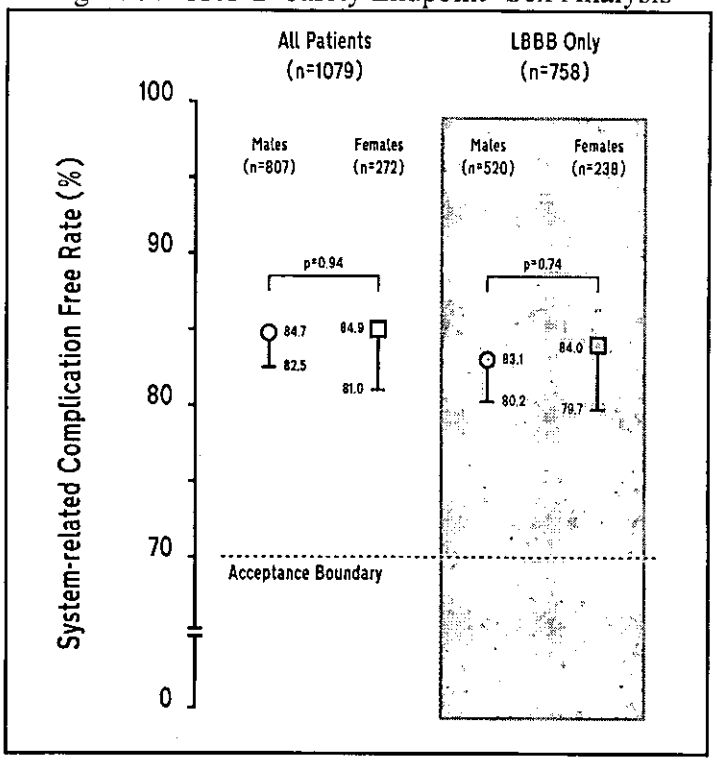
Characteristic	Measurement	Female (N=394)	Male (N=887)	P-value
Cardiac History				
NYHA Class/Ischemic [N (%)]	Class I Ischemic	15 (3.8)	128 (14.4)	<0.001
	Class II Ischemic	72 (18.3)	348 (39.2)	
	Class II Non-Ischemic	307 (77.9)	411 (46.3)	
Number of CHF Hospitalizations Prior to Enrollment [N (%)]	None	215 (55.7)	559 (63.9)	0.007
	1 – 2	157 (40.7)	276 (31.5)	
	3 or more	14 (3.6)	40 (4.6)	
Cardiac Risk Factors				
Atrial fibrillation > 1 month before enrollment	N (%)	26 (6.6)	114 (12.9)	<0.001
Coronary-bypass surgery	N (%)	32 (8.2)	250 (28.2)	<0.001
Cardiac Findings at Enrollment				
BUN >= 26 mg/dL	N (%)	70 (17.9)	227 (25.8)	0.002
Creatinine (mg/dl)	N	392	882	
	Mean ± SD	1.0 ± 0.3	1.2 ± 0.3	<0.001
	Range	0.4 – 2.2	0.5 - 2.7	
QRS duration >= 150 ms	N (%)	286 (72.6)	695 (78.4)	0.02
6 Minute Walk Distance (meters)	N	378	866	
	Mean ± SD	329 ± 108	379 ± 101	<0.001
	Range	31 - 686	0 - 744	
Euro Qol Index	N	392	882	
	Mean ± SD	0.82 ± 0.13	0.86 ± 0.13	<0.001
	Range	0.33 – 1.00	-0.04 - 1.00	
KCCQ Overall Summary Score	N	393	883	
	Mean ± SD	72 ± 18	78 ± 17	<0.001
	Range	20 - 100	10 - 100	
KCCQ Clinical Summary Score	N	393	883	
	Mean ± SD	77 ± 18	83 ± 16	<0.001
	Range	22 - 100	4 - 100	
KCCQ Quality of Life Score	N	393	883	

Characteristic	Measurement	Female (N=394)	Male (N=887)	P-value
	Mean ± SD	62 ± 23	69 ± 23	<0.001
	Range	0 - 100	0 - 100	
Echocardiographic or Doppler findings				
Left ventricular end-stystolic volume (ml)	N	392	882	
	Mean ± SD	156 ± 39	190 ± 55	<0.001
	Range	89 - 371	83 - 447	
Left ventricular end-diastolic volume (ml)	N	392	882	
	Mean ± SD	221 ± 48	264 ± 68	<0.001
	Range	134 - 448	145 - 571	
Medications				
Amiodarone	[N (%)]	7 (1.8)	72 (8.1)	<0.001
Beta Blockers	[N (%)]	380 (96.4)	824 (92.9)	0.01
Digitalis	[N (%)]	147 (37.3)	212 (23.9)	<0.001
Diuretic	[N (%)]	287 (72.8)	586 (66.1)	0.02
Statin	[N (%)]	197 (50.0)	614 (69.2)	<0.001

Safety Endpoint

The safety endpoint consisted of system-related complications occurring within 91 days post implant. The investigational system was considered safe if the system-related complication free rate was greater than 70%. The safety endpoint was met for both sexes in the full patient cohort as well as in the LBBB subpopulation as shown in Figure 9 below.

Figure 9: CRT-D Safety Endpoint- Sex Analysis



Primary Effectiveness Endpoint

MADIT-CRT assessed the effectiveness of CRT-D by the relative reduction in the risk of the combined endpoint of all-cause mortality or heart failure event, whichever occurred first, when compared to ICD.

Both men and women experienced a CRT-D benefit; however, women received a greater benefit than men. Both men and women with LBBB experienced a greater benefit with CRT-D than patients without LBBB as show in Figures 10 and 11 below.

Figure 10: Kaplan-Meier Curves of Time to All-Cause Mortality or HF Event by Sex (Full Patient Population)

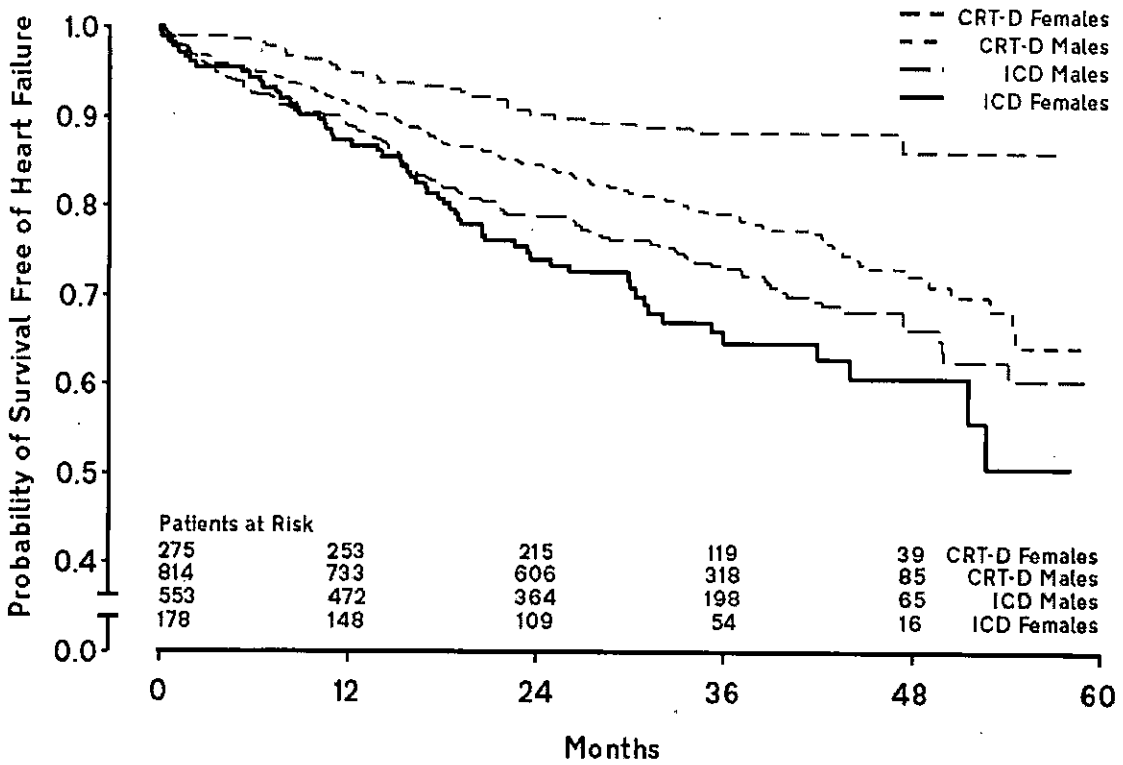
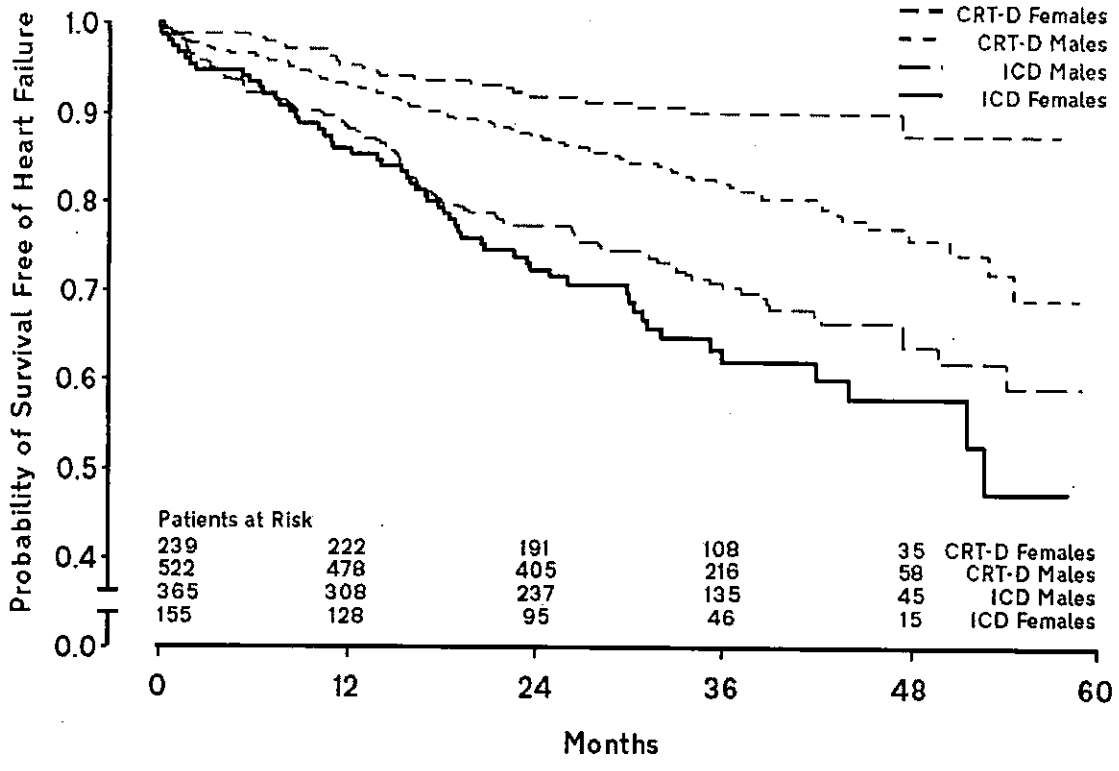


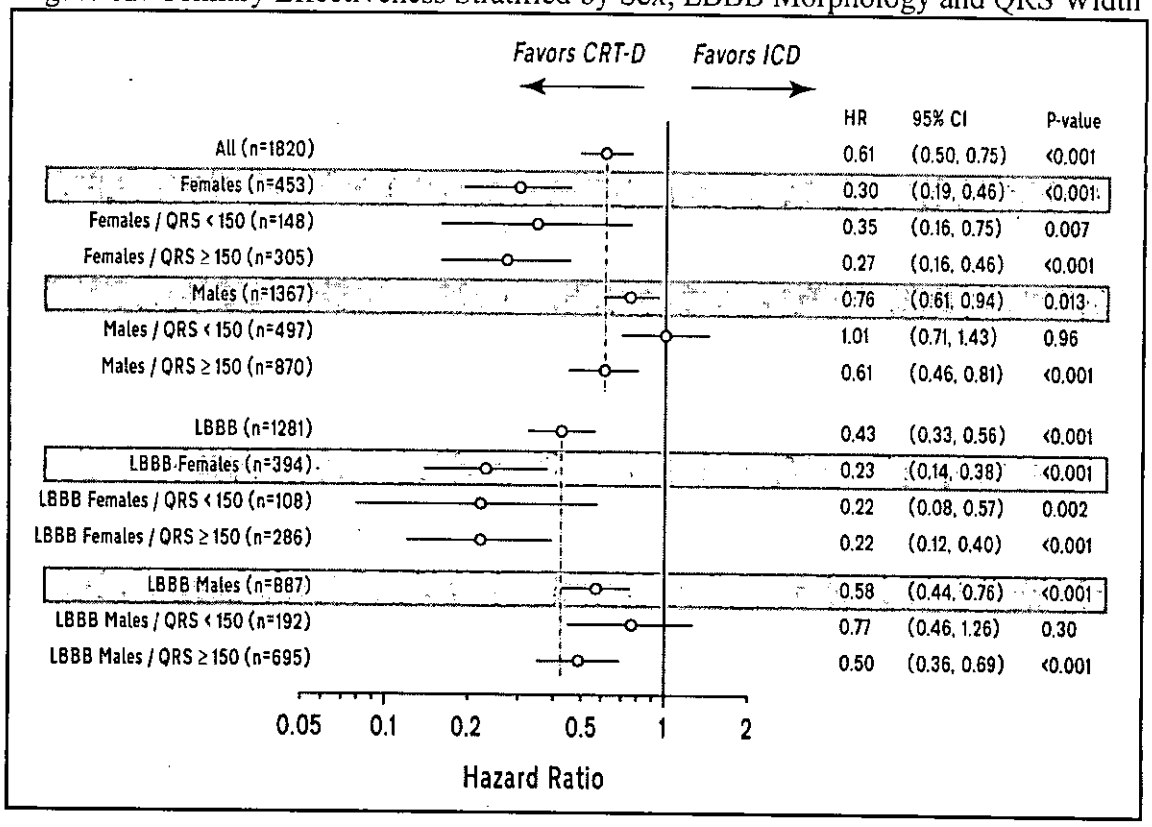
Figure 11: Kaplan-Meier Curves of Time to All-Cause Mortality or HF Event by Sex (LBBB Patient Sub-Population)



Primary Effectiveness Endpoint for Sex and QRS Subgroups

For both the full and the LBBB subpopulations, males with a wider QRS (≥150 ms) had a greater risk reduction with CRT-D than males with a narrow QRS. Women showed a more pronounced CRT-D benefit when compared to men, regardless of QRS width as show in Figure 12 below.

Figure 12: Primary Effectiveness Stratified by Sex, LBBB Morphology and QRS Width



Secondary Effectiveness Endpoint

MADIT-CRT also evaluated the effects of CRT-D, relative to ICD, on the recurrence of heart failure events over the full study period. The hypothesis was that the heart failure event rate for the CRT-D group would be less than that for the ICD group, with an average-rate ratio less than unity.

In the both the full and LBBB subpopulations, CRT-D reduced the risk of recurrent heart failure events for both men and women; however, the reduction was greater in women. The results are shown below in Table 22.

Table 22: Secondary Effectiveness Endpoint- Sex Analysis

		Hazard Ratio		
Population	**Covariate**	**Estimate**	**95% Confidence Interval**	**P-value**
All Patients	Males	0.74	(0.58, 0.95)	0.019
	Females	0.43	(0.27, 0.70)	<.001
LBBB Patients Only	Males	0.67	(0.46, 0.99)	0.044
	Females	0.32	(0.18, 0.55)	<.001

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on March 18, 2010, the Cardiovascular Devices Panel reviewed information presented by Boston Scientific and FDA, discussed the clinical data from the MADIT-CRT study, addressed the FDA questions, and voted unanimously (11-0) to recommend that the PMA application be "Approvable with Conditions." The panel recommended two (2) conditions of approval:

1. The Indications for Use include a statement to include only patients with LBBB (left bundle branch block) and stable sinus rhythm

2. A post approval study be conducted with a meaningful comparator group that assesses the predictive values of subgroups and risk factors for safety issues.

The panel found the system-related complications related to the CRT-D system and left ventricular lead to be consistent with standard medical practice for these commercially-available devices. The panel believed that the decrease in heart failure hospitalizations outweighs the increase in system-related complications. They discussed the fact that there is limited data capturing long term lead reliability, and this shortcoming is something that should be taken into consideration, perhaps in a post approval study.

In general the panel agreed that the lack of patient and physician blinding could have biased the results, but blinding would have been very difficult to maintain over an extended period of time. In addition, the sponsor did their best to develop a robust study given this limitation and used an independent, blinded committee to review the supporting heart failure event data.

The hazard ratio, although weak, does support using this device in NYHA Class I patients. The panel thought that it was important to note that these patients are already indicated for ICD therapy and do not represent the subset of ICD patients that are generally less healthy than the average NYHA Class I-II patients in general. Many of these patients have been or will become NYHA Class II patients. The panel agreed that patients with chronic atrial fibrillation do not respond well to CRT-D therapy. Patients with LBBB receive the most benefit from the device, although the analyses supporting this conclusion are post-hoc.

The panel felt that the proposed indications for use for the expanded patient population are too broad and should be limited to left bundle branch block and stable sinus rhythm for patients with NYHA Class I-II.

The materials for the panel meeting are available at the following link:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm204585.htm

The summary of the panel meeting is available at the following link: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM205855.pdf

B. FDA's Post-Panel Action

Following the panel meeting, FDA met with the company in order to discuss what data and analyses the company would need to submit in order to address the recommendations and questions from the panel discussion. The company subsequently submitted an updated clinical report, with additional analyses focused on the results in patients with left bundle branch block. These updated results are summarized in the clinical study section above.

Based on FDA's review of the additional information provided, FDA agreed with the panel's recommendation to limit the Indications for Use to patients with left bundle branch block. Based on the post-hoc analyses, the presence of left bundle branch block is an important indicator for the response to CRT-D.

FDA chose not to include the phrase "stable sinus rhythm" in the final indications for use, because this phrase was not used in the previous indications for use statements for other similar devices, even though multiple previous pivotal clinical studies conducted by various companies also required patients in stable sinus rhythm, excluding patients with atrial tachyarrhythmias. Because stable sinus rhythm was not included in other CRT-D's indications for use, FDA believed that the inclusion of such a restriction, in the absence of specific relevant findings in the MADIT-CRT study, would create inconsistencies in the labeling of CRT-D devices.

FDA provided feedback to the company to assist in developing two (2) appropriate post approval studies in order to gather additional long term supporting data to assess the predictive values of subgroups and risk factors for safety issues.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

In the full patient population evaluated during the MADIT-CRT clinical study, 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 rate was statistically significantly greater than 70% and therefore passed the pre-specified safety endpoint.

In the LBBB patient sub-population evaluated during the MADIT-CRT clinical study, the CRT-D system-related complication-free rate observed within 91 days post-implant was 83.4% with a lower one-sided 95% confidence bound of 81.0%. This rate was

statistically significantly greater than 70% and therefore passed the pre-specified safety endpoint.

In addition, FDA asked the company to present the safety data from the ICD control group and to compare that data to the CRT-D group. In the LBBB patient sub-population, the ICD control group system-related complication-free rate observed within 91 days post-implant was 93.1% with a lower one-sided 95% confidence bound of 91.0%. Overall, the rate of system-related complications in the CRT-D group was greater than the rate in the ICD control group. This difference in rates could be related to added complexity of the CRT-D system and the additional left ventricular lead. However, the increase in system-related complications was offset by a reduction in heart failure hospitalizations, and the reduction or prevention of heart failure hospitalizations is an important goal in the management of heart failure patients.

B. Effectiveness Conclusions

In the full patient population evaluated during the MADIT-CRT clinical study, CRT-D was associated with a 39% reduction in the relative risk of death or heart failure event as compared to ICD. However, there was no evidence of benefit in the non-LBBB patient sub-population as the results were predominately driven by the LBBB patient sub-population.

In the LBBB patient sub-population evaluated during the MADIT-CRT clinical study, which includes 70% of the patients enrolled into the MADIT-CRT clinical study, CRT-D was associated with a 57% reduction in the relative risk of death or heart failure event as compared to ICD. The primary effectiveness endpoint included all-cause mortality, out-patient heart failure events, and in-patient heart failure events. The primary endpoint event rates were 16% in the CRT-D group and 31% in the ICD group, with an absolute reduction of 15%. Most of the observed difference in primary endpoint events was related to the reduction in the rate of in-patient heart failure events (10% in the CRT-D group as compared to 22% in the ICD group).

During the review of the original data from the study (with non-LBBB and LBBB patients), FDA expressed concerns about the limited benefits observed in patients with QRS duration < 150 ms. In the original clinical report, patients with QRS duration < 150 ms had a 13% relative reduction in the risk of all-cause mortality and HF events. This value improved to 16% in an updated clinical report with extended follow-up. When restricted to only LBBB patients, the relative risk reduction in patients with QRS duration < 150 ms improves to 42%. Approximately 77% of patients with LBBB have a QRS duration ≥ 150 ms.

Similarly, during the review of the original data from the study, FDA expressed concerns about the limited enrollment (15% of the full MADIT-CRT population and 11% of the LBBB patient sub-population) and limited benefits observed in patients with NYHA Class I. In the original clinical report, NYHA Class I patients had a 28% relative reduction in the risk of the all-cause mortality and HF events. This value

improved to 40% in an updated clinical report with extended follow-up. When restricted to only LBBB patients, the relative risk reduction in patients with NYHA Class I improved again to 55%, which is very similar to results observed in the LBBB sub-population as a whole.

The consistency of these results supports the conclusion that LBBB was the best discriminator of benefit in MADIT-CRT. As a result of these findings, the requirement for LBBB is listed at the beginning of the expanded indication statement, before QRS duration, ejection fraction, and NYHA Class.

C. **Overall Conclusions**

Boston Scientific has provided valid scientific data and reasonable assurance of safety and effectiveness in the LBBB sub-population that CRT-D devices demonstrate a statistically significant reduction in the relative risk of the combined endpoint of all-cause mortality or first heart failure event by 57% as compared to ICD devices.

XIII. CDRH DECISION

CDRH issued an approval order on September 16, 2010. The final conditions of approval cited in the approval order include an agreement to conduct two (2) post approval studies:

- PAS I – This study will be conducted in collaboration with the ACC NCDR ICD Registry. Patients who meet the MADIT- CRT labeling indication (i.e., are NYHA functional class II with non-ischemic or ischemic cardiomyopathy and patients who are NYHA functional class I with ischemic cardiomyopathy with left ventricular dysfunction (EF $\leq$30%), prolonged intraventricular conduction (QRS $\geq$ 130 ms), and with LBBB) will be identified via the NCDR ICD registry. Mortality information will be collected for these patients over a 5 year post implant period. Patients in the registry implanted with a Boston Scientific CRT-D device will be compared to patients with a Boston Scientific ICD.

- PAS II – The primary purpose of a registry follow-up phase in the MADIT-CRT patient population is to evaluate whether or not a mortality reduction associated with CRT-D compared to ICD. While the study met its primary safety and effectiveness endpoints, a registry will reflect the durability of CRT-D over time. Accordingly, the proposed study is designed to provide an assessment of the long-term mortality benefits of CRT-D vs. ICD therapy in the MADIT-CRT patient population. Additionally, system-related information and patient status will be collected.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. New England Journal of Medicine 2009:361.