SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cardiac Resynchronization Therapy Defibrillator (CRT-D)

Device Trade Names:
Concerto CRT-D Model C154DWK
Consulta CRT-D Model D224TRK
Maximo II CRT-D Model D284TRK
Concerto II CRT-D Model D274TRK
Protecta XT CRT-D Model D314TRG
Protecta CRT-D Model D334TRG
Protecta XT CRT-D Model D314TRM
Protecta CRT-D Model D334TRM
Consulta CRT-D Model D204TRM
Maximo II CRT-D Model D264TRM

Applicant's Name and Address:
Medtronic, Inc.
Cardiac Rhythm Disease Management
8200 Coral Sea Street
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Date(s) of Panel Recommendation: December 7, 2011

Premarket Approval Application (PMA) Number: P010031/S232

Date of FDA Notice of Approval: April 4, 2012

Expedited: Not Applicable

The original PMA P010031, InSync ICD Model 7272, was approved on June 26, 2002 with an indication statement as follows:

> The InSync ICD Model 7272 is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction less than or equal to 35% and a QRS duration greater than or equal to 130 ms.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here: http://www.accessdata.fda.gov/cdrh_docs/pdf/P010031b.pdf.

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PMA supplement P010031/S018, (InSync III Marquis Model 7279, InSync Maximo Models 7303 and 7304, and InSync Sentry Models 7297 and 7299) was approved on April 8, 2005 where the indication statement was modified to read:

> The [name of the system] is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction less than or equal to 35% and a prolonged QRS duration.

PMA supplement P010031/S057, (Concerto CRT-D Models C154DWK and C164AWK) was approved on April 17, 2007 where the indication statement was further expanded to include atrial therapies and reads as follows:

> The [name of the system] is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. In addition, the device is indicated for use in patients with atrial tachyarrhythmias, or those patients who are at significant risk of developing atrial tachyarrhythmias. The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy and have a left ventricular ejection fraction ≤35% and a prolonged QRS duration.
>
> Atrial rhythm management features such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive Pacing (PMOP) are indicated for the suppression of atrial tachyarrhythmias in ICD-indicated patients with atrial septal lead placement and an ICD indication.

The current supplement (P010031/S232) was submitted to expand the indication for all currently marketed Medtronic CRT-Ds to include "Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II."

The U.S. Food and Drug Administration (FDA) approval history for the most recent Medtronic CRT-D devices is provided in Table 1.

Table 1: FDA Approval History for Medtronic CRT-D's

Name of Product	FDA Number	Date of FDA Approval
Concerto® Model C154DWK	P010031/S031	05/12/2006
Consulta™ Model D224TRK	P010031/S084	03/17/2008
Maximo® II Model D284TRK	P010031/S084	03/17/2008
Concerto® II Model D274TRK	P010031/S125	10/23/2008
Protecta™ XT Model D314TRG	P010031/S171	03/25/2011
Protecta™ Model D334TRG	P010031/S171	03/25/2011

Name of Product	FDA Number	Date of FDA Approval
Protecta™ XT Model D314TRM	P010031/S178	11/09/2011
Protecta™ Model D334TRM	P010031/S178	11/09/2011
Consulta® Model D204TRM	P010031/S176	01/09/2012
Maximo® II Model D264TRM	P010031/S176	01/09/2012

II. INDICATIONS FOR USE

The indications for use for the Concerto CRT-D Model C154DWK, Consulta CRT-D Model D224TRK, Concerto II CRT-D Model D274TRK, Protecta CRT-D Model D334TRG, Protecta CRT-D Model D334TRM, Protecta XT CRT-D Model D314TRG, Protecta XT CRT-D Model D314TRM, and Consulta CRT-D Model D204TRM are as follows:

> The [name of device] CRT-D system is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias and for providing cardiac resynchronization therapy in heart failure patients who remain symptomatic despite optimal medical therapy, and meet any of the following classifications:
>
> - New York Heart Association (NYHA) Functional Class III or IV and who have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.
> - Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II.
>
> The system is also indicated for use in patients with atrial tachyarrhythmias, or those patients who are at significant risk for developing atrial tachyarrhythmias.
> Atrial rhythm management features such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive (PMOP) are indicated for the suppression of atrial tachyarrhythmias in implantable cardioverter defibrillator (ICD)-indicated patients with atrial septal lead placement and an ICD indication.

The indication for use for Maximo II CRT-D Models D284TRK and D264TRM is as follows:

> The Maximo II CRT-D system is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias and for providing cardiac resynchronization therapy in heart failure patients who remain symptomatic despite optimal medical therapy, and meet any of the following classifications:
>
> - New York Heart Association (NYHA) Functional Class III or IV and who have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.
> - Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II.

III. CONTRAINDICATIONS

The contraindications for use for the Concerto CRT-D Model C154DWK, Consulta CRT-D Model D224TRK, Concerto II CRT-D Model D274TRK, Protecta CRT-D Model D334TRG, Protecta CRT-D Model D334TRM, Protecta XT CRT-D Model D314TRG, Protecta XT CRT-D Model D314TRM, and Consulta CRT-D Model D204TRM are as follows:

The [name of device] CRT-D system is contraindicated for patients experiencing tachyarrhythmias with transient or reversible causes including, but not limited to, the following: acute myocardial infarction, drug intoxication, drowning, electric shock, electrolyte imbalance, hypoxia, or sepsis.

The device is contraindicated for patients who have a unipolar pacemaker implanted.

The device is contraindicated for patients with incessant VT or VF.

The device is contraindicated for patients whose primary disorder is chronic atrial tachyarrhythmia with no concomitant VT or VF.

The Maximo II CRT-D Models D284TRK and D264TRM is CRT-D system is contraindicated for patients experiencing tachyarrhythmias with transient or reversible causes including, but not limited to, the following: acute myocardial infarction, drug intoxication, drowning, electric shock, electrolyte imbalance, hypoxia, or sepsis.

The device is contraindicated for patients who have a unipolar pacemaker implanted.

The device is contraindicated for patients with incessant VT or VF.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions for Medtronic CRT-D's are provided in the product labeling.

V. DEVICE DESCRIPTION

Medtronic CRT-D devices are multi-programmable, dual chamber implantable cardioverter defibrillators with biventricular pacing features for cardiac resynchronization. The CRT-D device along with pacing leads and the defibrillation lead constitute the implantable portion of the system.

Medtronic CRT-D devices monitor and regulate the patient's heart rate by providing single or dual chamber rate-responsive bradycardia pacing, sequential biventricular pacing, ventricular tachyarrhythmia therapies, and atrial tachyarrhythmia therapies if available.

The device senses the electrical activity of the patient's heart using the electrodes of the implanted atrial and right ventricular leads. It then analyzes the heart rhythm based on selectable detection parameters.

The devices automatically detect ventricular tachyarrhythmias (VT/VF) and provide treatment with defibrillation, cardioversion, and antitachycardia pacing therapies. The devices also automatically detect atrial tachyarrhythmias (AT/AF) and provide treatment with cardioversion and antitachycardia pacing therapies, if available. Simultaneous or sequential biventricular pacing is used to provide patients with cardiac resynchronization therapy. The devices respond to bradyarrhythmias by providing bradycardia pacing therapies.

The device also provides diagnostics and monitoring information that assist with system evaluation and patient care.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices and procedures for patients exhibiting left bundle branch block (LBBB) with a QRS duration $\geq$ 130 ms, left ventricular ejection fraction $\leq$ 30%, and NYHA Functional Class II, include modifications to diet, exercise, lifestyle changes, and pharmacological therapy.

In addition, there are commercially available CRT-D devices that are indicated for patients who receive stable optimal pharmacologic therapy for heart failure and who meet the following classifications: left bundle branch block (LBBB) with QRS duration $\geq$ 130 ms, EF $\leq$ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure.

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

The above referenced Medtronic CRT-D devices are currently marketed in the following countries: Argentina, Australia, Belarus, Bosnia-Herzegovina, Brazil, Canada, China, Columbia, Croatia, Europe (EU Countries), Israel, Kazakhstan, Macedonia, Mexico, New Zealand, Russia, Serbia, Singapore, South Africa, Taiwan, Thailand, Turkey, Ukraine, Uruguay, and Venezuela. Medtronic first received FDA approval for CRT-D devices on June 26, 2002 under PMA P010031. None of these devices have been withdrawn from marketing anywhere for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the transvenous leads and pacing systems:

- acceleration of tachyarrhythmias (caused by device)
- air embolism
- bleeding
- body rejection phenomena, including local tissue reaction
- cardiac dissection
- cardiac perforation
- cardiac tamponade
- chronic nerve damage
- constrictive pericarditis
- death
- device migration
- endocarditis
- erosion
- excessive fibrotic tissue growth
- extrusion
- fibrillation or other arrhythmias
- fluid accumulation
- formation of hematomas/seromas or cysts
- heart block
- heart wall or vein wall rupture
- hemothorax
- infection
- keloid formation
- lead abrasion and discontinuity
- lead migration/dislodgement
- mortality due to inability to deliver therapy
- muscle and/or nerve stimulation
- myocardial damage
- myocardial irritability
- myopotential sensing
- pericardial effusion
- pericardial rub
- pneumothorax
- poor connection of the lead to the device which may lead to oversensing, undersensing, or a loss of therapy
- threshold elevation
- thrombotic embolism
- thrombosis
- tissue necrosis
- valve damage (particularly in fragile hearts)
- venous occlusion
- venous perforation

An additional potential adverse event associated with the use of transvenous left ventricular pacing leads is coronary sinus dissection.

Additional potential adverse events associated with the use of ICD systems include, but are not limited to, the following events:

- inappropriate shocks
- potential mortality due to inability to defibrillate
- shunting current of insulating myocardium during defibrillation

Patients susceptible to frequent shocks despite medical management could develop psychological intolerance to an ICD system that might include the following conditions:

- dependency
- depression
- fear of premature battery depletion
- fear of shocking while conscious
- fear that shocking capability may be lost
- imagined shocking (phantom shock)

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

IX. SUMMARY OF PRECLINICAL STUDIES

Medtronic CRT-D systems are commercially available. 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 in the applications listed in Table 1 above.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

This section includes summaries of the Medtronic-sponsored "REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction" (REVERSE) Clinical Study which was conducted under IDE G040004, and the University of Ottawa Heart Institute-sponsored "Resynchronization / defibrillation for Ambulatory heart Failure Trial" (RAFT) as outlined in Table 2.

Table 2: REVERSE and RAFT Clinical Studies

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects
REVERSE (IDE G040004)	Prospective, randomized, controlled, two-arm, double-blind, multi-center clinical trial	Evaluate the effectiveness of CRT in NYHA Class I and II, Stage C subjects with LVEF ≤ 40% and QRS ≥ 120 ms	73	684 enrolled 621 successfully implanted 610 randomized and analyzed
RAFT	Prospective, randomized, controlled, two-arm, double-blind, multi-center clinical trial	Evaluate the effectiveness of CRT-D in NYHA Class II and III subjects with LVEF ≤ 30 % and QRS ≥ 120 ms	34	1798 enrolled and randomized 1787 successfully implanted 1798 analyzed

Demonstration of the clinical effectiveness for expanding the indication for use for Medtronic CRT-D systems to NYHA Class II patients with left branch bundle block, QRS duration ≥ 130 ms and LVEF ≤ 30% is based on a subset of post-hoc results from the REVERSE and RAFT studies in which commercially available Medtronic devices were used. Determination of criteria for the "expanded indication population" was based on inclusion criteria common to both studies, and further narrowed to LBBB patients with QRS ≥ 130 ms as a stronger benefit was observed in these subgroups. A comparison of study designs is provided below in Table 3.

Table 3: REVERSE and RAFT Comparison of Study Designs

	REVERSE	RAFT
Study Design	Randomized CRT-D or CRT-P vs. no CRT Double-blinded	Randomized CRT-D vs. ICD Double-blinded
Implant	Implanted with CRT-D or CRT-P device prior to randomization. Control group (CRT OFF) did not have CRT functionality turned on.	Randomized prior to implant, then implanted with CRT-D or ICD.
Randomization Ratio	2:1 CRT ON : CRT OFF	1:1 CRT-D : ICD
Size	n=610 U.S., Europe, Canada	n=1798 Canada, Western Europe, Turkey, Australia
Duration	12 months (U.S. and Canada) 24 months (Europe only) At these time points, all subjects had CRT turned on and were followed for a total of 5 years.	Minimum18 months Average follow-up 40 months Subjects stayed in their randomized arm throughout the study.
NYHA Class	I or II (ACC/AHA Stage C)	II or III
LVEF	≤40%	≤30%
QRS Duration	≥120ms	≥120ms
Primary Endpoint	HF Clinical Composite (proportion worsened)	Total mortality and heart failure hospitalization

The following sections will provide an overview of the REVERSE study and results and the RAFT study and results. Where appropriate, results for the expanded indication population are provided following the full cohort results.

REVERSE Clinical Study

A. Study Design

Overview

The REVERSE study was a prospective, randomized, double-blinded, multi-center global study conducted in the United States, Canada, and Europe. It was designed to determine whether biventricular pacing limited the progression of heart failure in a subject's clinical status as compared to optimal medical therapy alone in subjects with asymptomatic or mild heart failure (NYHA Class I and II, Stage C), ventricular dyssynchrony (QRS $\geq$120 ms), and reduced systolic left ventricular ejection fraction (LVEF $\leq$40%).

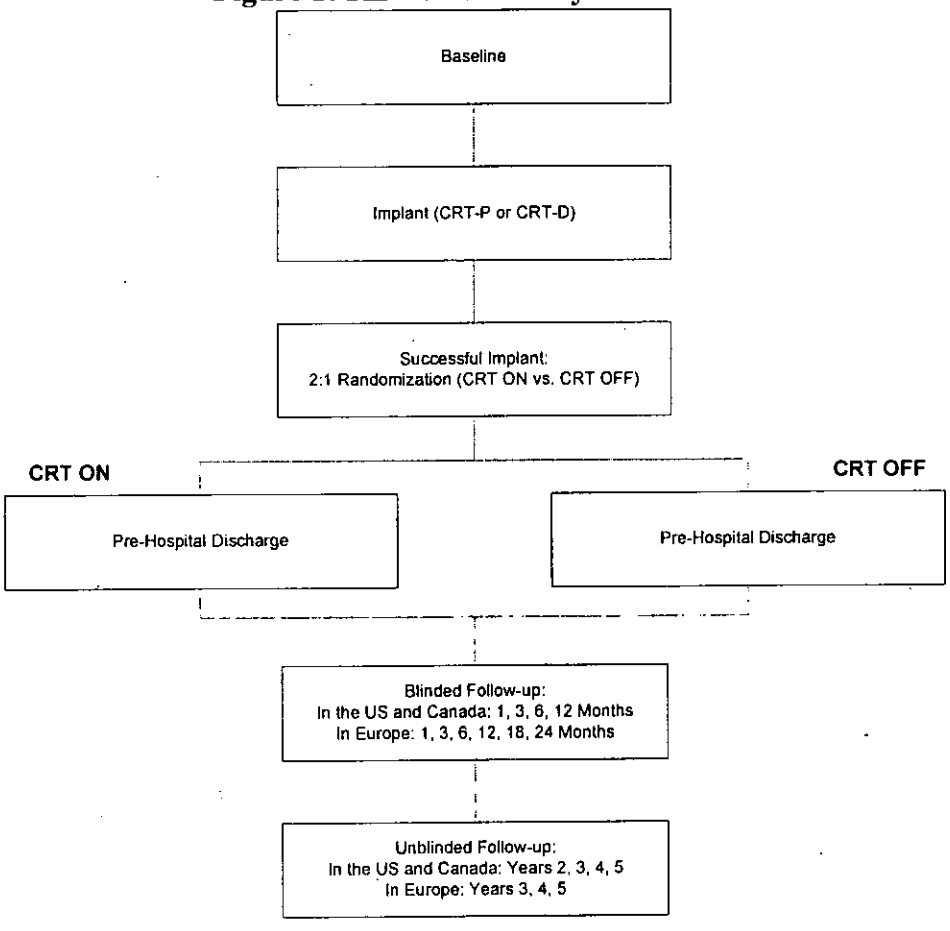
Subjects were enrolled between September 3, 2004 and September 11, 2006. The REVERSE database for this PMA supplement reflected data that occurred on or before March 5, 2010 and were received by June 13, 2010. Updates to the database were allowed until the final database freeze on June 14, 2010. A total of 684 subjects signed informed consent forms at 73 investigational sites, with 610 subjects undergoing randomization.

Enrolled subjects were implanted with a Medtronic CRT-P or CRT-D system (depending on ICD indication), and following successful implant were randomized in a 2:1 fashion to one of two (2) study arms: biventricular pacing in conjunction with optimal medical therapy (CRT ON) or optimal medical therapy alone (CRT OFF).

In the U.S. and Canada, subjects were unblinded at 12 months and continued to be seen annually through 5 years of follow-up. European subjects were unblinded at 24 months and were seen annually thereafter until 5 years. It was recommended that all subjects have CRT programmed on at the conclusion of the blinded follow-up.

The study schematic for visits is shown below in Figure 1.

Figure 1: REVERSE Study Schematic



Statistical Methods

The primary objective of this study was to compare the Clinical Composite Response percent worsened between subjects in the CRT ON and CRT OFF groups. The Clinical Composite Response utilizes clinically meaningful endpoints including mortality, hospitalization for heart failure, crossover, NYHA Functional Class, and the Patient Global Assessment, to categorize subjects as improved, unchanged, or worsened.

Specifically, the following hypothesis was used:

H_0: %(Worsened) $_{CRT\ ON}$ = %(Worsened) $_{CRT\ OFF}$
H_A: %(Worsened) $_{CRT\ ON}$ ≠ %(Worsened) $_{CRT\ OFF}$

Where %(Worsened) = percent of subjects with a worsened Clinical Composite Response at 12 months post-randomization.

Left ventricular end systolic volume index (LVESVi) was selected as a prospectively powered secondary endpoint. Assessments were made by comparing the change in LVESVi from baseline to 12 months between the CRT ON group and the CRT OFF group.

The prospectively powered secondary endpoint, LVESVi was tested with the following hypothesis:

H_0: $\Delta(\text{LVESVi})_{\text{CRT ON}} = \Delta(\text{LVESVi})_{\text{CRT OFF}}$
H_A: $\Delta(\text{LVESVi})_{\text{CRT ON}} \neq \Delta(\text{LVESVi})_{\text{CRT OFF}}$

Where Δ(LVESVi) is the change in LVESVi from baseline to 12 months.

All statistical analysis was done using frequentist methods. There were no interim looks at the primary endpoint.

Assumptions for the sample size calculation were based on data from NYHA Class II subjects in the MIRACLE ICD study[6]. It was assumed that 22.0% of CRT ON subjects, and 34.1% of CRT OFF subjects worsen. Under a two-sided type I error of $\alpha = 0.05$, and power of 80%, a minimum of 512 subjects with a Clinical Composite Response were needed. Because nearly all subjects were expected to receive a Clinical Composite Response, the post-randomization attrition rate was assumed to be zero. The attrition from signing of the informed consent (enrollment) to randomization included dropouts between informed consent and implant attempt, unsuccessful implants, and dropouts between implant and randomization, resulting in an assumed attrition rate of 25% and total enrolled sample size requirement of approximately (512/0.75) 683 subjects.

Missing data was not imputed in this study. When a subject had missing data, that subject was not included in the analysis where the data was missing.

Study Oversight

To reduce bias, echocardiographic data were interpreted at core laboratories that were not informed of subjects' randomization assignment. There were two (2) geographical echo core laboratories. Centers in the U.S. and Canada sent echo recordings to the U.S. Echo Core Lab and centers in Europe sent echo data to the European Echo Core Lab.

An Adverse Event Advisory Committee (AEAC)/ Endpoint Committee was established by Medtronic to assess, review, and classify all adverse events and deaths during the clinical study. The committee also reviewed and adjudicated HF relatedness of all-cause healthcare utilization data excluding Emergency Room visits. An HF hospitalization was defined as an overnight hospital admission, where the admission date and discharge date are different, and the Adverse Event Advisory Committee (AEAC) adjudicated the event as heart failure related. Committee members were blinded to the randomization assignment of the subjects. The committee determined the relatedness of all adverse events and deaths to the system, procedure, therapy, and heart failure (for hospitalizations). The committee also adjudicated heart failure relatedness of all crossovers.

A Data Monitoring Committee (DMC) was convened at six (6) month intervals during the blinded period of the study to review adverse events, to address potential safety issues, and to provide recommendations for study continuation.

Control Group

The study was designed to determine whether biventricular pacing with or without ICD therapy, in addition to optimal medical therapy, limited the progression of heart failure in a subject's clinical status as compared to optimal medical therapy alone. The control group in the study received a CRT-P or CRT-D implant, but CRT features were turned off. These subjects (along with the CRT ON group) were to receive optimal medical therapy. All subjects were implanted to allow for double-blinding.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the REVERSE study was limited to patients who met the following key inclusion criteria:

   - NYHA Functional Class I or II with current American College of Cardiology/ American Heart Association (ACC/AHA) Stage C classification as confirmed by the documented consensus of two qualified individuals within 30 days prior to enrollment or during the baseline assessment. Stage C classification includes subjects who have current or prior symptoms of heart failure associated with underlying structural heart disease. Qualified individuals must include at least one cardiologist and another physician or a heart failure clinician/ nurse. A minimum of one classifying individual must be recorded on the Blinding Log. If the two qualified individuals assessing the NYHA Functional classification do not reach a consensus, the subject is not eligible.
   - Ventricular dyssynchrony by QRS duration ≥120 ms (at Baseline or within the 30 days prior to enrollment)
   - History of a left ventricular ejection fraction ≤40%, which is confirmed at the baseline echo
   - Stable optimal medical regimen, which minimally includes an Angiotensin Converting Enzyme- Inhibitor (ACE-I) or Angiotensin Receptor Blockers (ARB) at therapeutic dose for 30 days prior to enrollment, if tolerated, and a beta blocker (BB) that is approved and indicated for HF within the geography for 90 days prior to enrollment, if tolerated, with a stable dosage for 30 days prior to enrollment. If the subject is intolerant of ACE-I or BB, documented evidence must be available. If anti-aldosterone therapy is needed in the NYHA Functional Class II subjects, it must be initiated and optimized prior to enrollment. Eplerenone requires dosage stability for 30 days prior to enrollment. Diuretics may be used as necessary to keep the subject euvolemic. Therapeutic equivalence for ACE-I substitutions is allowed within the enrollment stability timelines.
   - History of a left ventricular end diastolic diameter (LVEDD) ≥55 mm or the equivalent value via LVEDD Index (i.e., LVEDDi ≥ 2.8 cm/m2), which is confirmed at the baseline echo

- Indicated for an ICD as defined by the associated geography current at the time of enrollment, for those subjects that will be implanted with a CRT-D system

Patients were not permitted to enroll in the REVERSE study if they met any of the following key exclusion criteria:

- Classified as NYHA Functional Class III or IV in the 90 days prior to enrollment
- Decompensation of heart failure requiring hospitalization for the treatment of heart failure within the 90 days prior to enrollment
- Unstable angina, acute MI, CABG or PTCA within the 90 days prior to enrollment
- Requires permanent cardiac pacing
- Continuous or intermittent (i.e., more than two infusions per week) intravenous inotropic drug therapy
- Chronic (permanent) or persistent atrial arrhythmias. Chronic (permanent) atrial arrhythmias are defined as cases of long-standing atrial fibrillation (e.g., greater than 1 year) in which cardioversion has not been indicated or attempted. Persistent atrial arrhythmias are defined as recurrent atrial fibrillation (i.e., 2 episodes or more) that does not self-terminate
- Cardioversion for atrial fibrillation or paroxysmal atrial fibrillation event within the past 30 days
- CRT-P, pacemaker, ICD or CRT-D device implanted previously or currently, except in cases where previously implanted non-CRT ICD device lifetime counters indicate the device is 95% free of ventricular and atrial pacing. If the ICD device or the subject records cannot provide this data, the subject is not eligible.

2. Follow-up Schedule

Clinical assessments occurred at baseline, implant, pre-hospital discharge, 1 month, 3 months, 6 months, 12 months, 18 months (Europe only), and then at 2, 3, 4 and 5 years. Clinical data was also collected for unscheduled follow-up visits, health care utilizations, subject exit (including death), and system modifications. Adverse events were recorded at all visits. Visit descriptions are outlined in Table 4 below.

Table 4: REVERSE Description of Visits

Visit	Description
Baseline	Subject consent, subject history and symptoms, NYHA and ACC/AHA classification, echo, blood tests, 6-minute hall walk, Quality of Life (QOL), Electrocardiogram (ECG)
Implant	System implant, testing, and programming
Pre-hospital Discharge	Medications, chest x-ray, echo, final device programming, ECG, device interrogation save-to-disk
Blinded Follow-up	QOL, patient global assessment, 6-minute hall walk, physical assessment,

Visit	Description
(through 12 months for North American patients and through 2 years for European patients)	NYHA and ACC/AHA classification, ECG, device interrogation save-to-disk, lead electrical data, medications, healthcare utilization, adverse events, previous blood tests (if available), echo at 6, 12, 18 (Europe only), and 24 months (Europe only)
Unblinded Follow-up (all follow-ups after the blinded period)	QOL, 6-minute hall walk, physical assessment, NYHA and ACC/AHA classification, device interrogation save-to-disk, healthcare utilization, adverse events, echo

3. Clinical Endpoints

As CRT is a well-established therapy for which the risks are known, there was no pre-specified safety endpoint required for the study.

The primary effectiveness endpoint was the HF Clinical Composite Response measured at 12 months. The REVERSE study evaluated the proportion of subjects in each randomization group who were characterized as "Worsened" at 12 months as compared to baseline.

Left ventricular end systolic volume index (LVESVi) was selected as a prospectively powered secondary endpoint to assess its relationship to outcomes in the NYHA Class I and II Stage C heart failure population. The change in LVESVi from baseline to 12 months was compared between the CRT ON group and CRT OFF group.

Success of the primary effectiveness endpoint was defined as a greater percentage of subjects with a worsened Clinical Composite Response in the CRT OFF group compared to the CRT ON group, with the difference being statistically significant.

Success of the key secondary endpoint was defined as a greater reduction in LVESVi at 12 months compared to baseline in the CRT ON group than the CRT OFF group, with the difference being statistically significant.

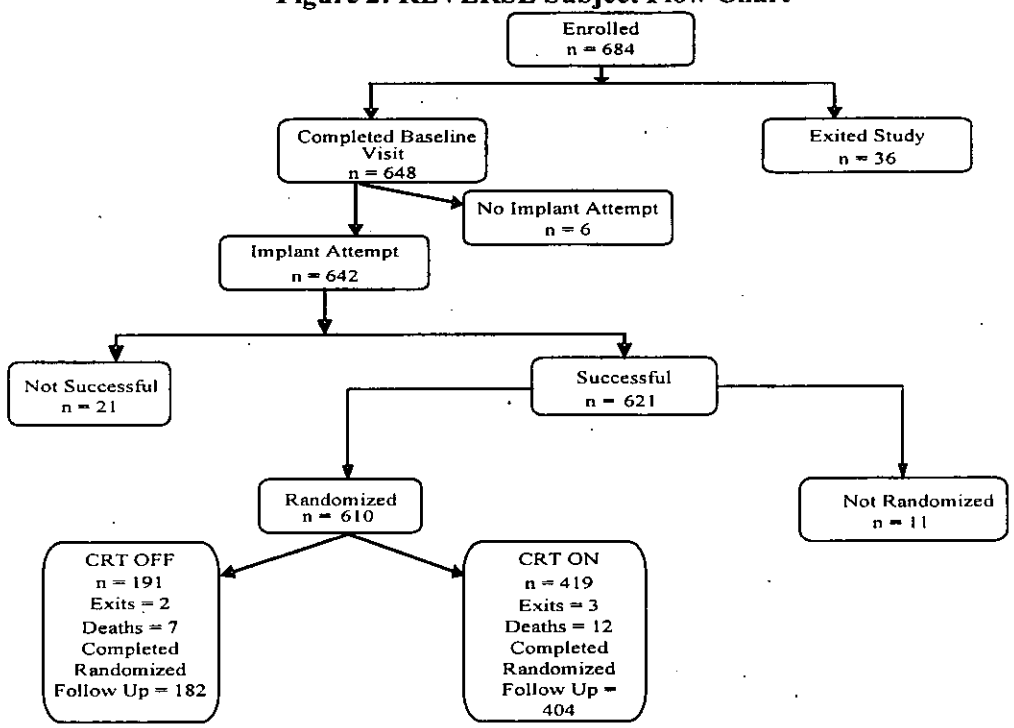
B. Accountability of PMA Cohort

At the time of the database lock, 684 subjects had been enrolled in the REVERSE study, 621 of which were successfully implanted. Of the 621 successfully implanted subjects, 610 were randomized. All 610 randomized subjects were included in the study analyses following completion of the randomized period of the study (the 12-month visit for U.S. and Canadian subjects, and the 24-month visit for European subjects).

The status of all subjects enrolled in the study is summarized below in Figure 2. Of the 621 successfully implanted subjects, 11 (1.8%) were not randomized. Six (6) were exited, one (1) subject died, and the other four (4) were followed for safety

(three (3) were subjects who received epicardial leads and one (1) was a subject who developed atrial arrhythmias during the implant).

Figure 2: REVERSE Subject Flow Chart



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a heart failure studies performed in the U.S. The baseline demographics for the 610 randomized subjects are provided in **Table 5**.

Consistent with the demographics of systolic heart failure patients, the subjects randomized in REVERSE were predominantly male (78.5%). The average age at baseline was 62.5 years. The subjects had an average LVEF of 26.7% and LVEDD of 66.9 mm according to readings at the centers. The majority of subjects were NYHA Class II (82.5%).

Table 5: REVERSE Baseline Demographics – Full Cohort

Subject Characteristic	CRT OFF (n= 191)	CRT ON (n= 419)
Male	80% (152)	78% (327)
Age (years)	61.8 ± 11.6	62.9 ± 10.6
Ethnicity		
Black	3% (6)	7% (28)
American Indian	0% (0)	<1% (1)
Asian	1% (2)	<1% (1)
White	86% (164)	83% (346)
Hispanic	1% (2)	2% (8)
Hawaiian	0% (0)	<1% (1)
Other	1% (2)	0% (0)
Not specified	8% (15)	8% (34)
LVEF (%)	26.4 ± 7.1	26.8 ± 7.0
LVEDD (mm)	67.4 ± 8.9	66.7 ± 8.9
QRS Duration (ms)	154 ± 24	153 ± 21
QRS Morphology Type		
RBBB	10% (20)	9% (37)
LBBB	59% (59)	61% (256)
IVCD	30% (58)	29% (123)
Ischemic	51% (97)	56% (236)
Device		
CRT-D	85% (163)	82% (345)
CRT-P	15% (28)	18% (74)
NYHA Classification		
Class I	17% (32)	18% (75)
Class II	83% (159)	82% (344)
Beta blocker	94% (179)	96% (401)
ACE-I/ARB	97% (186)	96% (404)
Diuretic	77% (148)	81% (339)

For the expanded indication patient population (left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II), 179 (29%) REVERSE subjects meet the labeling criteria. Baseline demographics for the expanded indication population from REVERSE are presented in Table 6.

Table 6: REVERSE Baseline Demographics - Expanded Indication Population

Subject Characteristic	CRT OFF (n= 60)	CRT ON (n= 119)
Male	73% (44)	76% (91)
Age (years)	58.7 ± 12.1	62.9 ± 11.6
Ethnicity		
Black	3% (2)	8% (9)
American Indian	0% (0)	0% (0)
Asian	2% (1)	0% (0)
White	80% (48)	76% (90)
Hispanic	2% (1)	4% (5)
Hawaiian	0% (0)	0% (0)
Other	0% (0)	0% (0)
Not specified	13% (8)	13% (15)
LVEF (%)	22.8 ± 5.6	22.7 ± 5.1
LVEDD	70.3 ± 9.8	68.5 ± 9.2
QRS duration (ms)	168 ± 19	165 ± 19
QRS Morphology Type		
RBBB	0% (0)	0% (0)
LBBB	100% (60)	100% (119)
IVCD	0% (0)	0% (0)
Ischemic	32% (19)	45% (53)
Device		
CRT-D	100% (60)	100% (119)
CRT-P	0% (0)	0% (0)
NYHA Classification		
Class I	0% (0)	0% (0)
Class II	100% (60)	100% (119)
Beta blocker	93% (56)	97% (116)
ACE-I/ARB	97% (58)	97% (116)
Diuretic	78% (47)	81% (96)

D. Safety and Effectiveness Results

1. Safety Results

There was no pre-specified safety endpoint for the REVERSE study. However, adverse events and deaths were collected in the study and adjudicated by a blinded Adverse Event Advisory Committee (AEAC). All events were classified as either complications or observations. The following definitions were used:

Complication: An adverse event that results in invasive intervention, or the termination of significant device function regardless of other treatments. Intravenous (IV) and intramuscular (IM) drug therapies are considered invasive treatments.

Observation: Any adverse event that is not a complication.

Adverse events that occurred in the study are reported in **Error! Reference source not found.**. A summary of deaths occurring during the randomized period is provided in Table 8. Additionally, an analysis of time to first post-implant LV lead-related complication is presented in Figure 3.

Adverse events that occurred in the PMA clinical study:
There were 660 implant attempts in a total of 642 subjects. This included 621 successful implants and 39 unsuccessful implant attempts (16 subjects had two (2) or more attempts). A total of 608 adverse events were classified as procedure-, system-, or therapy-related at the time of the data cut-off. A summary of all adverse event types where there was at least one (1) complication reported is provided in **Error! Reference source not found.**, which is sorted in descending order based on the total number of events.

Table 7: REVERSE Procedure, System, or Therapy-related Adverse Events – Full Cohort

	Complications		Observations		Total	
Event Description	**# Events**	**# Subjects**	**# Events**	**# Subjects**	**# Events**	**# Subjects**
Device related complications	20	19 (3.1%)	73	62 (10.0%)	93	76 (12.2%)
Medical device change	71	70 (11.3%)	0	0 (0.0%)	71	70 (11.3%)
LV lead dislodgement	47	44 (7.1%)	1	1 (0.2%)	48	44 (7.1%)
Device lead damage	43	42 (6.8%)	1	1 (0.2%)	44	43 (6.9%)
Lead malfunction events	24	22 (3.5%)	20	18 (2.9%)	44	39 (6.3%)
Implant site reactions	10	9 (1.4%)	33	31 (5.0%)	43	39 (6.3%)
Supraventricular arrhythmias	14	13 (2.1%)	11	10 (1.6%)	25	23 (3.7%)
Coronary sinus dissection	2	2 (0.3%)	17	17 (2.7%)	19	19 (3.1%)
RV lead dislodgement	18	17 (2.7%)	0	0 (0.0%)	18	17 (2.7%)
RA lead dislodgement	16	15 (2.4%)	2	2 (0.3%)	18	16 (2.6%)
Implant site infection	5	4 (0.6%)	11	11 (1.8%)	16	15 (2.4%)

	Complications		Observations		Total	
Event Description	**# Events**	**# Subjects**	**# Events**	**# Subjects**	**# Events**	**# Subjects**
Pneumothorax and pleural effusions	5	4 (0.6%)	10	10 (1.6%)	15	13 (2.1%)
Pericardial disorders	8	8 (1.3%)	4	4 (0.6%)	12	12 (1.9%)
Atrioventricular block third degree	4	4 (0.6%)	7	7 (1.1%)	11	10 (1.6%)
Cardiac failure	5	5 (0.8%)	5	5 (0.8%)	10	10 (1.6%)
Hypotension	6	6 (1.0%)	2	2 (0.3%)	8	8 (1.3%)
Ventricular arrhythmias and cardiac arrest	6	6 (1.0%)	2	2 (0.3%)	8	8 (1.3%)
Peripheral thrombosis	4	4 (0.6%)	1	1 (0.2%)	5	5 (0.8%)
Non-site specific procedural complications	2	2 (0.3%)	3	3 (0.5%)	5	5 (0.8%)
Electrical reset of device	1	1 (0.2%)	4	4 (0.6%)	5	5 (0.8%)
Adverse drug reaction	3	3 (0.5%)	1	1 (0.2%)	4	4 (0.6%)
Allergic reaction	2	2 (0.3%)	2	2 (0.3%)	4	4 (0.6%)
Sudden cardiac death	3	3 (0.5%)	0	0 (0.0%)	3	3 (0.5%)
Renal failure	3	3 (0.5%)	0	0 (0.0%)	3	3 (0.5%)
Cardiac perforation	3	3 (0.5%)	0	0 (0.0%)	3	3 (0.5%)
Syncope vasovagal	2	2 (0.3%)	1	1 (0.2%)	3	3 (0.5%)
Device electrical finding	1	1 (0.2%)	2	2 (0.3%)	3	3 (0.5%)
Lower respiratory tract signs and symptoms	1	1 (0.2%)	2	2 (0.3%)	3	3 (0.5%)
Endocarditis	2	2 (0.3%)	0	0 (0.0%)	2	2 (0.3%)
Acute pulmonary edema	2	2 (0.3%)	0	0 (0.0%)	2	2 (0.3%)
Pyrexia	1	1 (0.2%)	1	1 (0.2%)	2	2 (0.3%)
Pericarditis	1	1 (0.2%)	1	1 (0.2%)	2	1 (0.2%)
Vertigo CNS origin	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.2%)
Vascular pseudoaneurysm	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.2%)
Death	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.2%)
Hematoma evacuation	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.2%)
Gastrointestinal hemorrhage	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.2%)
Muscle strain	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.2%)
Intracardiac thrombus	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.2%)

	Complications		Observations		Total	
Event Description	**# Events**	**# Subjects**	**# Events**	**# Subjects**	**# Events**	**# Subjects**
Influenza	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.2%)
Total*	343	230 (37.0%)	265	196 (31.6%)	608	338 (54.4%)

* Note that the total number of observations (265) and total number of adverse events (608) at the bottom of the table includes all events, including 48 observations that were not associated with a complication. The main body of the table did not include entries for these events, which were not associated with at least one complication, in order to reduce the length of the table.

During the randomized period, 19 deaths occurred in the study: 7 in the CRT OFF group (3.7%) and 12 in the CRT ON group (2.9%). All deaths were adjudicated by the Adverse Event Advisory Committee (AEAC). Per the Clinical Investigation Plan, if insufficient information was available to classify a death as sudden cardiac, non-sudden cardiac, or non-cardiac, the death was classified as unknown.

The most common cause of death during the randomized period was progressive heart failure (4 of 19 deaths). At least 8 of the 19 (42.1%) deaths were from non-cardiac causes.

Death information for all randomized subjects who died prior to their 12-month follow-up (U.S. and Canada) or their 24-month follow-up (Europe) is summarized in Table 8.

Table 8: REVERSE Cause of Death Summary – Full Cohort

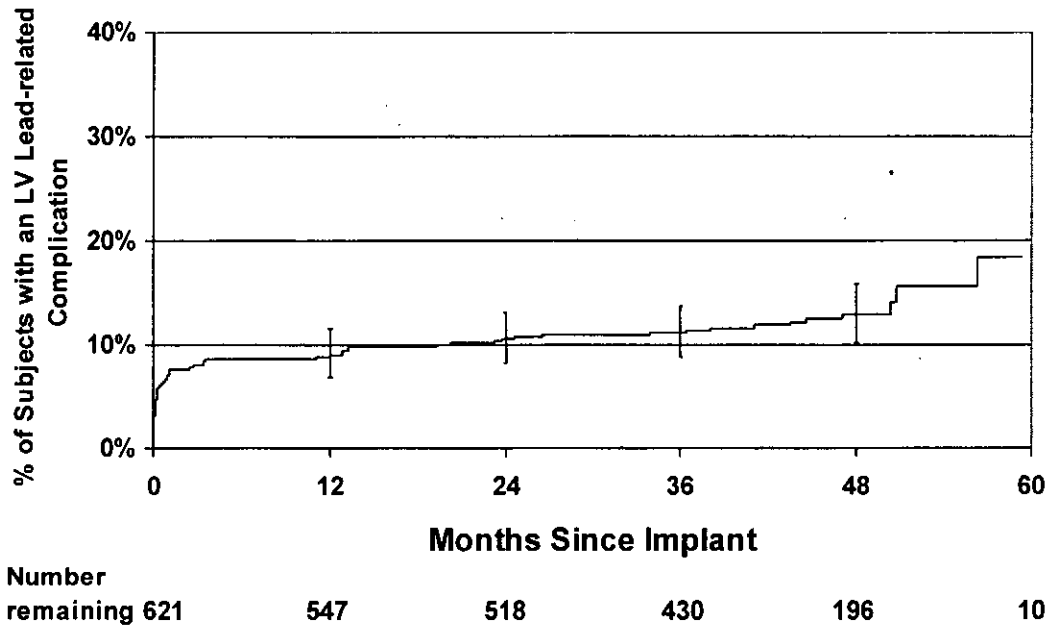
	CRT OFF (n=191)	CRT ON (n=419)	Total (n=610)
Non-cardiac	3 (43%)	5 (42%)	8 (42%)
Sudden cardiac	2 (29%)	4 (33%)	6 (32%)
Non-sudden cardiac, HF related	1 (14%)	3 (25%)	4 (21%)
Unknown	1 (14%)	0 (0%)	1 (5%)
Total	7 (100%)	12 (100%)	19 (100%)

All subjects in the trial received a CRT-P or CRT-D device, depending on whether they were indicated for an ICD. Since the majority of REVERSE subjects were already indicated for an ICD[1] at the time of enrollment (83%), the incremental risk for these subjects was the implantation of the LV lead and potential subsequent complications. All subjects in the trial received an LV lead; however, the LV pacing feature was not activated for subjects in the CRT OFF group until the end of their randomization period (12 months in the U.S. and Canada, and 24 months in Europe).

Among the 621 subjects that were successfully implanted with the CRT system, 77 had a total of 92 LV lead-related complications after their successful implant. The two (2) most common LV lead-related complications, accounting for 70% of these types of events, were LV lead dislodgement and diaphragmatic stimulation.

A Kaplan-Meier curve for the time to the first LV lead-related complication post-implant is shown in Figure 3 (all implanted subjects are included from their time of implant regardless of randomization). The majority of these events occurred within 3 months post-implant, at which time the LV lead complication rate was 8.1% (95% confidence interval: 6.1-10.4%). At 12 months, the LV lead-related complication rate was 9.1% (95% confidence interval: 7.0-11.5%). At 24 months, the LV lead-related complication rate was 10.6% (95% confidence interval: 8.3-13.2%). At 48 months, the rate was 12.8% (95% confidence interval: 10.2-15.8%).

Figure 3: REVERSE Time to First Post-implant LV Lead-related Complication



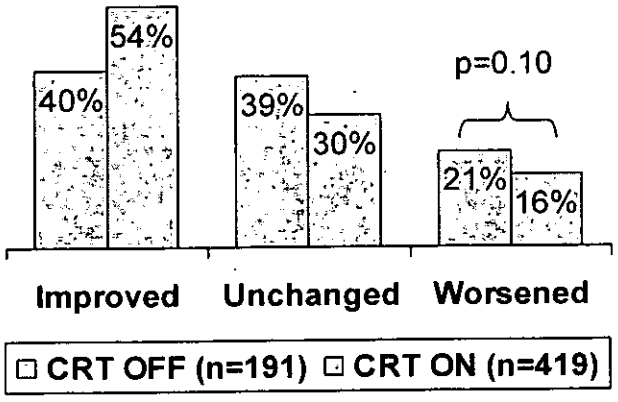
2. Effectiveness Results

The analysis of effectiveness was based on 610 evaluable patients for the Clinical Composite Response at the 12-month time point, as well as the prospectively powered secondary endpoint of LVESVi at the 12-month time point. Key effectiveness outcomes, including additional analyses supporting effectiveness, are presented below.

The primary endpoint for the study was the Clinical Composite Response (CCR). A CCR was recorded at 12 months for all 610 randomized subjects. The Clinical Investigation Plan (CIP) pre-specified that a comparison would be made between the two (2) randomization groups based on the percentage of subjects worsened.

In the full cohort, 21% of the CRT OFF group subjects worsened vs. 16% of the CRT ON group subjects as shown in Figure 4. Although CRT ON resulted in a more favorable response, it did not achieve statistical significance at 12 months (p=0.10).

Figure 4: REVERSE Clinical Composite Response Distribution of Responses Analysis at 12-Months – Full Cohort



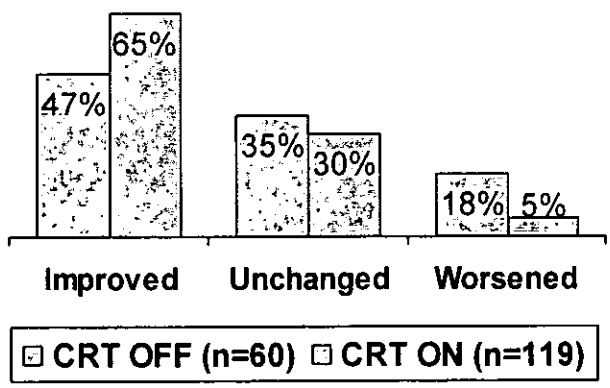
Additional details on the Clinical Composite Response results at 12 months for the full cohort are provided in Table 9. Note that a subject is only indicated in the sub-category in the highest row which was met (e.g., a subject who died and had a HF-hospitalization is only listed in the "Death" row). The total percentage of subjects improving their NYHA class can be found by adding the number improving both patient global assessment and NYHA class and those improving just NYHA class.

Table 9: REVERSE Detailed Clinical Composite Response at 12 Months – Full Cohort (post hoc analysis)

Clinical Composite Response	CRT OFF (n=191)	CRT ON (n=419)
WORSENED	41 (21%)	67 (16%)
Death	3 (2%)	9 (2%)
Hospitalized for worsening HF	14 (7%)	14 (3%)
Crossover due to worsening HF	5 (3%)	1 (<1%)
Moderately or Markedly Worse Patient Global Assessment and Worsened NYHA	0 (0%)	2 (<1%)
Worsened NYHA	18 (9%)	38 (9%)
Moderately or Markedly Worse Patient Global Assessment	1 (1%)	3 (1%)
IMPROVED	76 (40%)	228 (54%)
Moderately or Markedly Improved Patient Global Assessment and Improved NYHA	11 (6%)	69 (16%)
Improved NYHA	28 (15%)	59 (14%)
Moderately or Markedly Improved Patient Global Assessment Only	37 (19%)	100 (24%)
UNCHANGED	74 (39%)	124 (30%)

The primary endpoint was also analyzed for the expanded indication population. As shown in Figure 5, 18% of subjects in the CRT OFF group had a worsened CCR vs. 5% of the subjects in the CRT ON group.

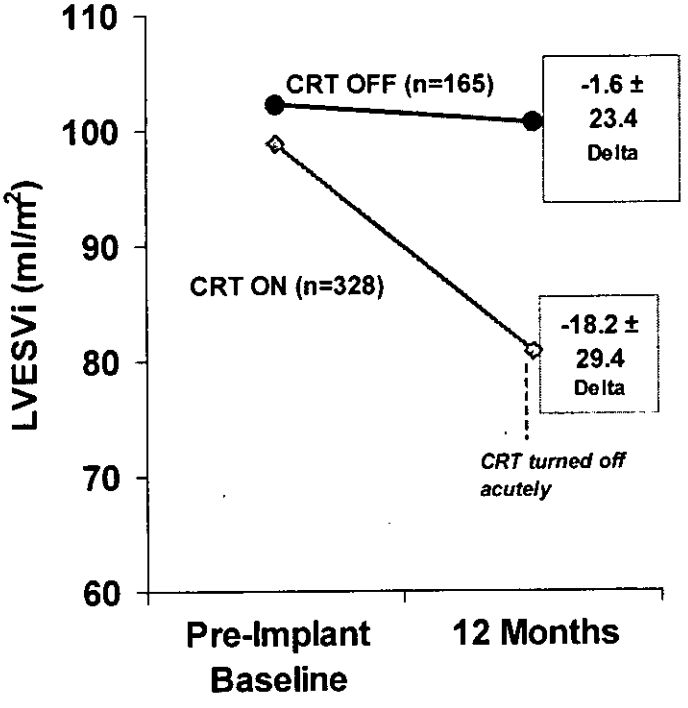
Figure 5: REVERSE Clinical Composite Response 12-month Results – Expanded Indication Population



Left ventricular end systolic volume index (LVESVi) was a prospectively powered secondary endpoint for the study. Figure 6 shows the LVESVi results

for the echo performed at 12 months post-implant as compared to baseline for the full cohort. CRT was programmed off for all subjects while the 12-month echo was performed in order to eliminate the potential acute effects of CRT on the LVESVi measurement. In the full cohort, the CRT OFF subjects averaged a 1.6 ml/m^2 reduction in LVESVi over 12 months while the CRT ON subjects averaged an 18.2 ml/m^2 reduction.

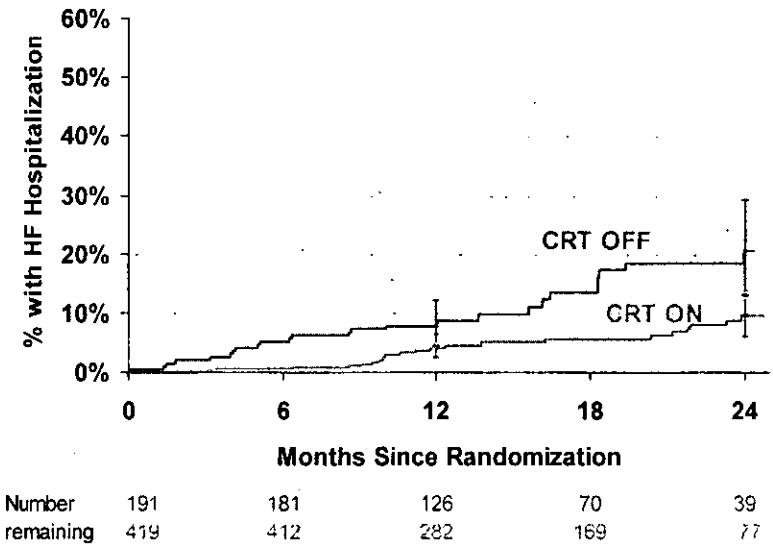
Figure 6: REVERSE LVESVi (ml/m^2): Baseline vs. 12 Months (CRT programmed off) – Full Cohort



Time to first heart failure (HF) hospitalization was compared between the CRT ON and CRT OFF groups as part of the secondary healthcare utilization objective. All hospitalizations were adjudicated by the Adverse Event Advisory Committee (AEAC) to be either HF related or not HF related. Figure 7 shows the time to the first HF hospitalization for the full cohort. At 12 months, the rate in the CRT OFF group was 7.9%, compared to the rate in the CRT ON group of 4.2%. At 24 months, the rates were 20.5% in CRT OFF and 9.5% in CRT ON.

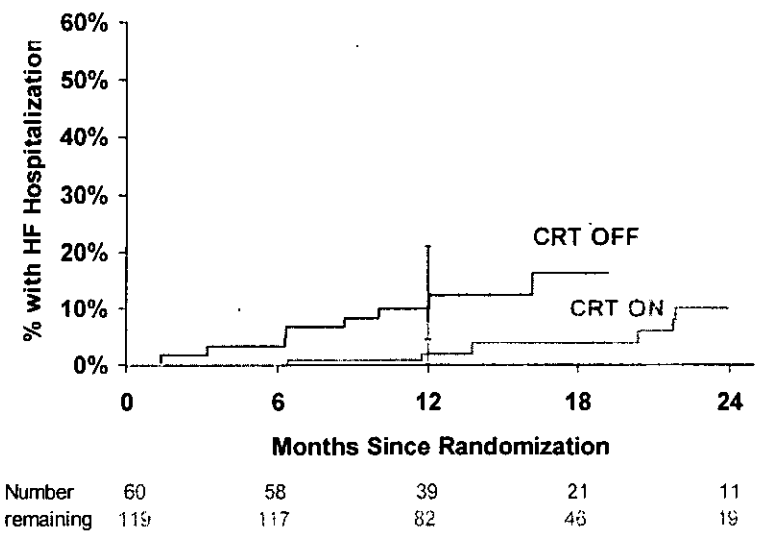
For Figure 7 through Figure 10, note that U.S. and Canadian subjects were unblinded at 12 months, while European subjects were unblinded at 24 months. The poolability analysis of U.S. and OUS patients showed differences in baseline characteristics and results. Therefore, the results at 24 months might not be applicable to U.S. patients.

Figure 7: REVERSE Time to First HF Hospitalization – Full Cohort (post-hoc analysis)



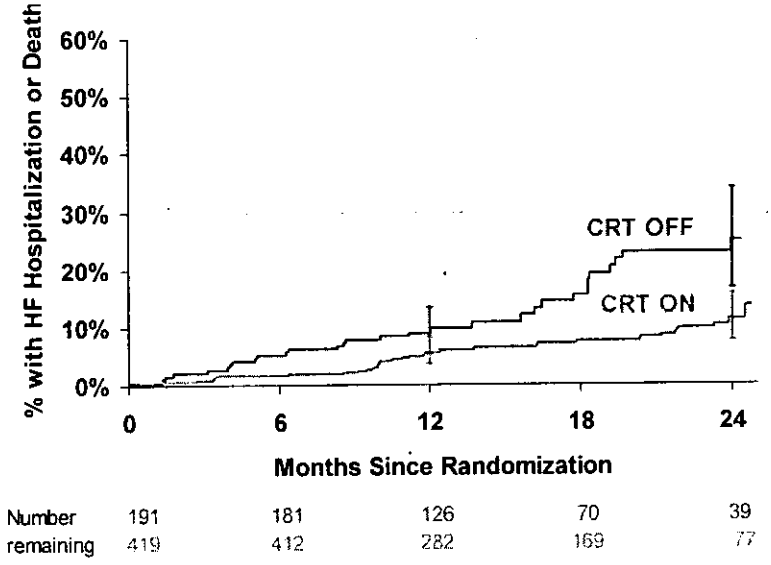
Time to first HF hospitalization was also analyzed for the expanded indication population (Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II) as shown in Figure 8.

Figure 8: REVERSE Time to First HF Hospitalization – Expanded Indication Population (post-hoc analysis)



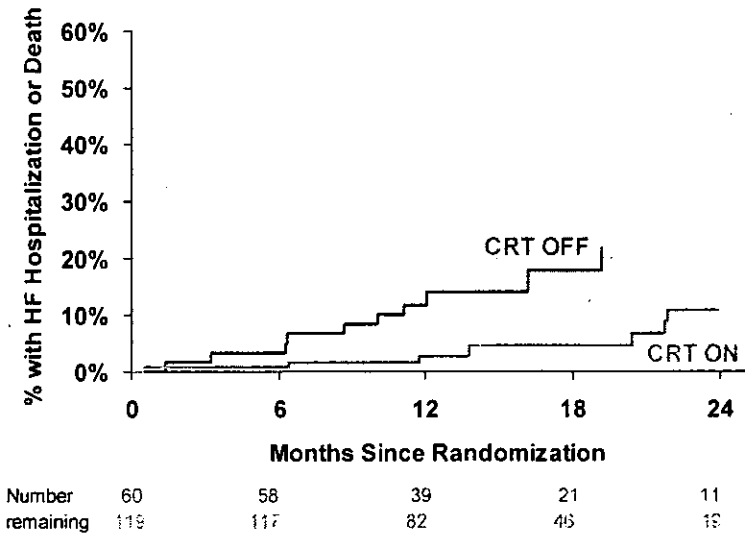
Although not pre-specified, the time to first heart failure hospitalization or all-cause death was analyzed to align with other CRT trials, including RAFT. Figure 9 depicts the time to the first HF hospitalization or all-cause death for CRT OFF vs. CRT ON in the full cohort. United States and Canadian subjects were unblinded at 12 months and were censored from the curves at that time. At 12 months, the CRT OFF group had a rate of 8.9% and CRT ON had a rate of 5.6%. At 24 months, the rates were 25.0% in the CRT OFF group, and 11.3% in the CRT ON group.

Figure 9: REVERSE Time to First HF Hospitalization or All-cause Death – Full Cohort (post-hoc analysis)



Time to first HF hospitalization or all-cause death was also analyzed for the expanded indication population (Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II) as shown in Figure 10.

Figure 10: REVERSE Time to First HF Hospitalization or All-cause Death - Expanded Indication Population (post-hoc analysis)



3. Subgroup Analyses

Additional subgroup analyses on ischemic/non-ischemic subjects, U.S./non-U.S. subjects, and ICD/non-ICD subjects were pre-specified to be performed for the primary endpoint and prospectively powered secondary endpoint.

Subgroup analyses performed for the full cohort for the Clinical Composite Response worsened and time to first HF hospitalization or all-cause death are summarized in Figure 11 and Figure 13. Lines represent 95% confidence intervals, which should be interpreted with the understanding that no subgroup was powered to see a difference between CRT OFF and CRT ON. In addition, post-hoc subgroup analyses of QRS duration evaluated as a continuous variable, along with categorical analysis in groups of 10 ms (120-129, 130-139, etc.) are presented in Figure 12 and Figure 14.

Figure 11: REVERSE Clinical Composite Response Worsened Subgroup Analysis – Full Cohort (post-hoc analysis)

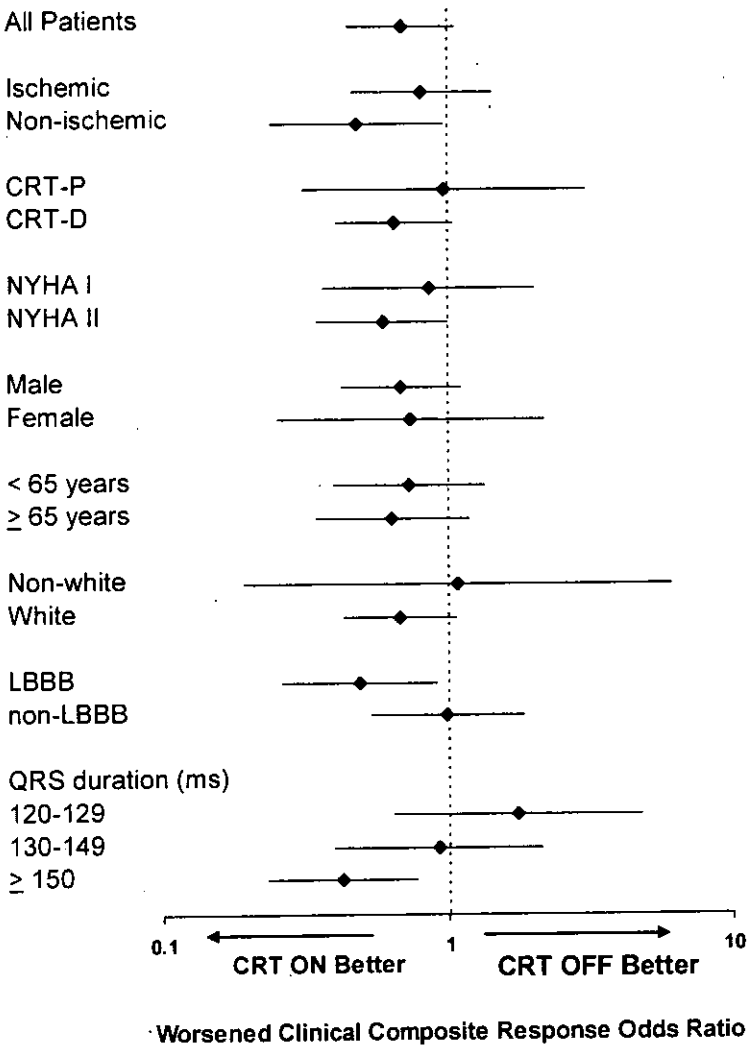


Figure 12: REVERSE Clinical Composite Response Worsened Subgroup Analysis: QRS Duration Odds Ratio – Full Cohort (post-hoc analysis)

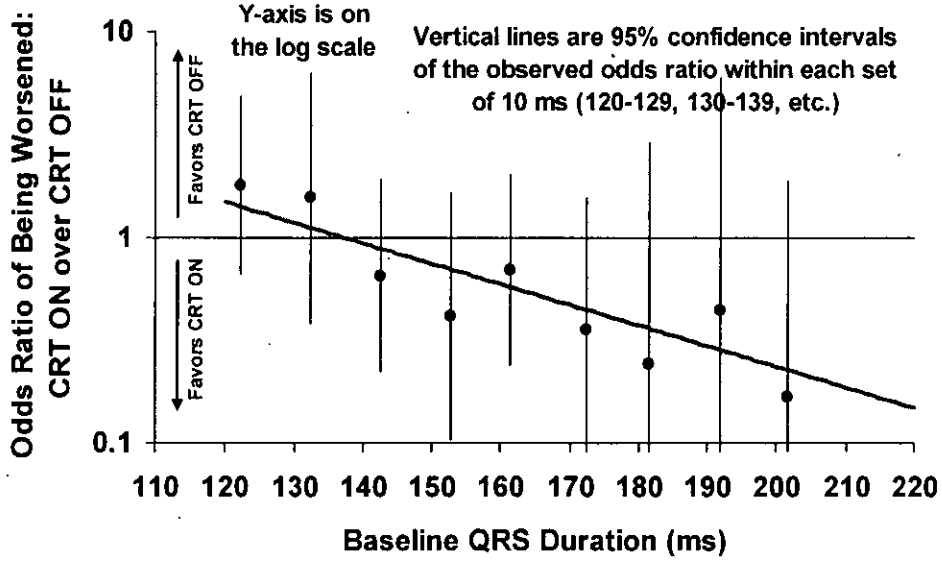


Figure 13: REVERSE Time to First HF Hospitalization or All-cause Death Subgroup Analysis – Full Cohort (post-hoc analysis)

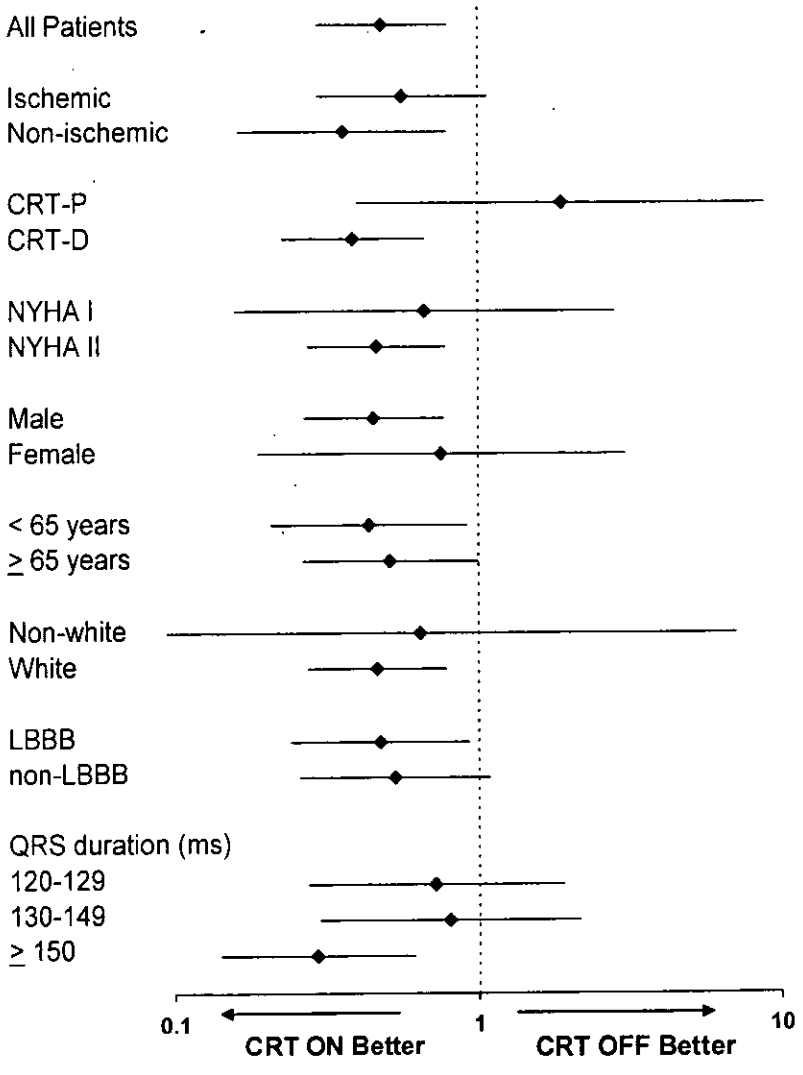
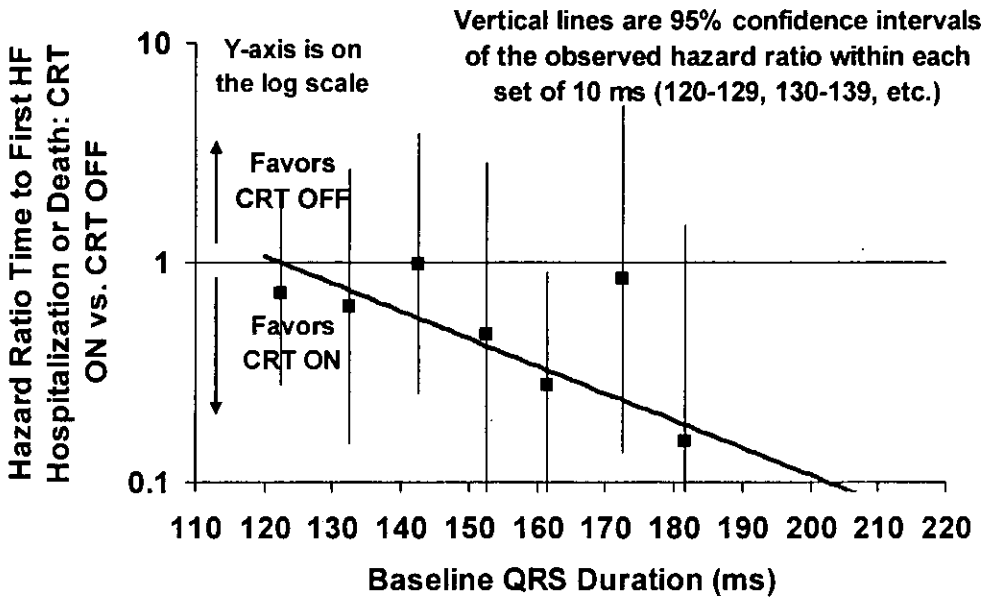
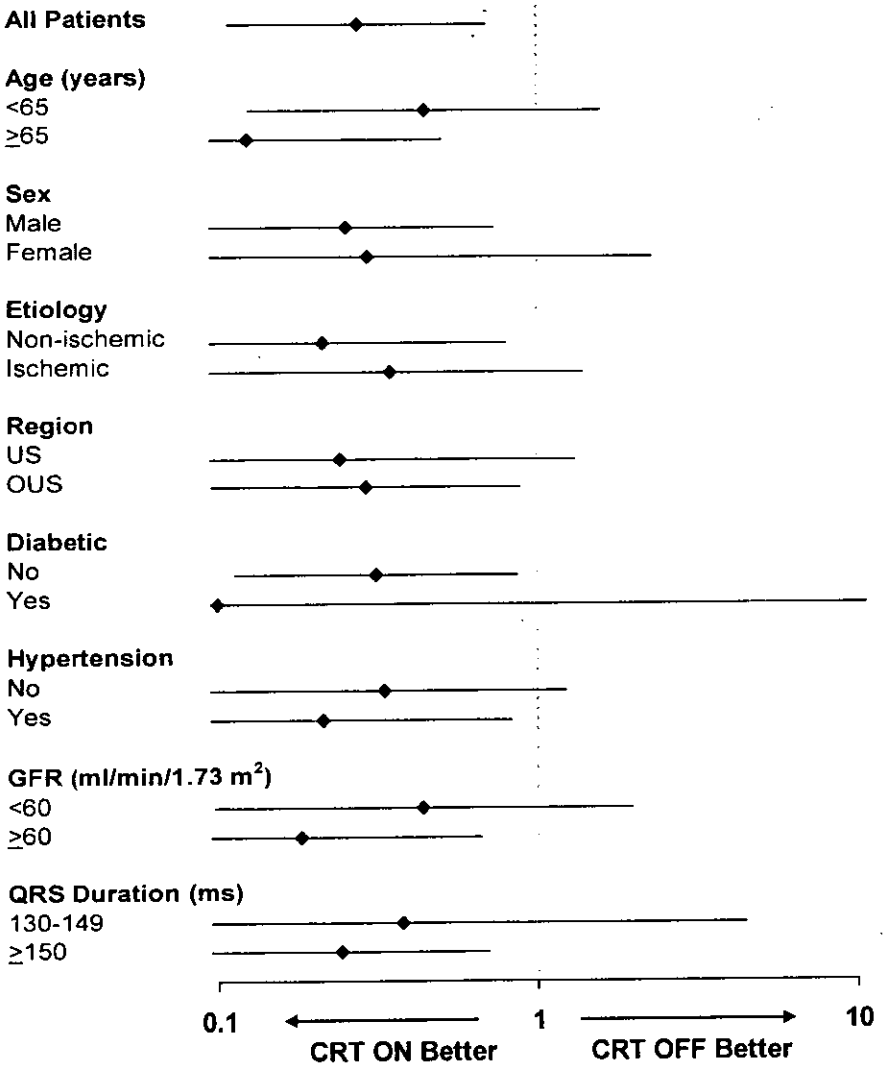


Figure 14: REVERSE Time to First HF Hospitalization or All-cause Death Subgroup Analysis: QRS Duration Odds Ratio – Full Cohort (post-hoc analysis)



Additionally, a subgroup analysis for time to first HF hospitalization or death was performed for the expanded indication population (Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II) as summarized in Figure 15. Lines represent 95% confidence intervals, which should be interpreted with the understanding that no subgroup was powered to see a difference between CRT OFF and CRT ON.

Figure 15: REVERSE Time to First HF Hospitalization or All-cause Death Subgroup Analysis – Expanded Indication Population (post-hoc analysis)



Gender Analysis

Additional subgroup analyses were performed by gender. In REVERSE, both men and women demonstrated improvement with CRT ON over CRT OFF. There was no significant difference in results for the primary endpoint, the Clinical Composite Response. There were some differences in baseline characteristics between males and females indicated by p-values < 0.05 as shown in Table 10.

Table 10: REVERSE Baseline Demographics by Gender – Full Cohort

Subject Characteristic	Female (n= 131)	Male (n= 479)	p-value
Age (years)	62.4 ± 11.2	62.6 ± 10.9	0.86
Ethnicity			
Black	11% (15)	4% (19)	0.01
American Indian	<1% (1)	0% (0)	
Asian	0% (0)	<1% (3)	
White	79% (104)	85% (406)	
Hispanic	<1% (1)	2% (9)	
Hawaiian	0% (0)	<1% (1)	
Other	0% (0)	<1% (2)	
Not specified	8% (10)	8% (38)	
LVEF (%)	27.1 ± 7.2	26.6 ± 7.0	0.44
LVEDD (mm)	62.6 ± 7.9	68.1 ± 8.8	<0.001
QRS duration (ms)	153 ± 20	153 ± 23	0.78
QRS Morphology Type			
RBBB	2% (2)	11% (55)	
LBBB	79% (103)	56% (266)	<0.001
IVCD	20% (26)	32% (155)	
Ischemic	30% (39)	61% (294)	<0.001
Device			
CRT-D	79% (104)	84% (404)	0.19
CRT-P	21% (27)	16% (75)	
NYHA Classification			
Class I	14% (18)	19% (89)	0.24
Class II	86% (113)	81% (390)	
Beta blocker	98% (129)	94% (451)	0.04
ACE-I/ARB	97% (127)	97% (463)	1.00
Diuretic	80% (105)	80% (382)	1.00

Baseline characteristics by gender for the expanded indication population from REVERSE are presented in Table 11.

Table 11: REVERSE Baseline Demographics by Gender - Expanded Indication Population

Subject Characteristic	Female (n= 44, 25%)	Male (n= 135, 75%)	p-value
Male	0% (0)	100% (135)	<0.001
Age (years)	61.4 ± 11.2	61.5 ± 12.1	0.95
Ethnicity			
Black	11% (5)	4% (6)	0.37
American Indian	0% (0)	0% (0)	
Asian	0% (0)	<1% (1)	
White	73% (32)	79% (106)	
Hispanic	2% (1)	4% (5)	
Hawaiian	0% (0)	0% (0)	
Other	0% (0)	0% (0)	
Not specified	14% (6)	13% (17)	
LVEF (%)	22.8 ± 5.7	22.7 ± 5.2	0.91
LVEDD (mm)	64.5 ± 7.0	70.6 ± 9.6	<0.001
QRS Duration (ms)	159 ± 17	168 ± 19	0.004
QRS Morphology Type			
RBBB	0% (0)	0% (0)	
LBBB	100% (44)	100% (135)	1.00
IVCD	0% (0)	0% (0)	
Ischemic	30% (13)	44% (59)	0.11
Device			
CRT-D	100% (44)	100% (135)	1.00
CRT-P	0% (0)	0% (0)	
NYHA Classification			
Class I	0% (0)	0% (0)	1.00
Class II	100% (44)	100% (135)	
Beta blocker	98% (43)	96% (129)	1.00
ACE-I/ARB	98% (43)	97% (131)	1.00
Diuretic	77% (34)	81% (109)	0.67

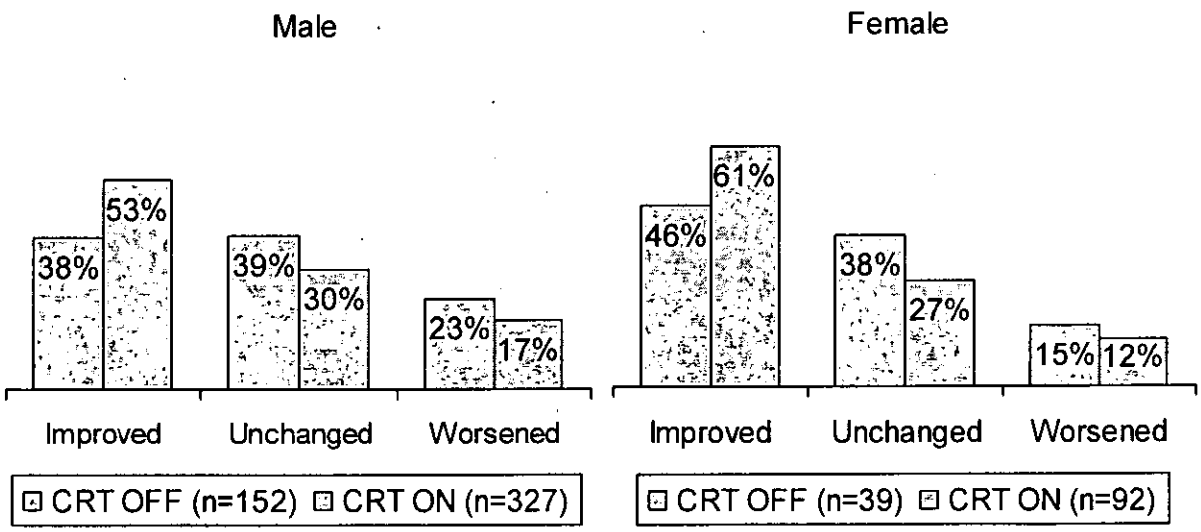
The proportion of female subjects enrolled in the REVERSE study is lower than the gender-specific incidence or prevalence of heart failure in this patient population; however, similar to what has been observed in other trials of CRT.[2] In the REVERSE full cohort, 79% of subjects were male and 21 % were female, and in the expanded indication population, 75% were male and 25% were female.

Analyses by gender for the REVERSE full cohort and REVERSE expanded indication population are presented below for the primary CCR percent worsened endpoint and key secondary LVESVi endpoint. P-values comparing male and female results are from the interaction term of logistic regression (Clinical Composite Score), linear regression (LVESVi), or Cox proportional hazards (time to first HF hospitalization or death) models. Terms fit in the models were randomization, gender, and their interaction.

Primary Endpoint

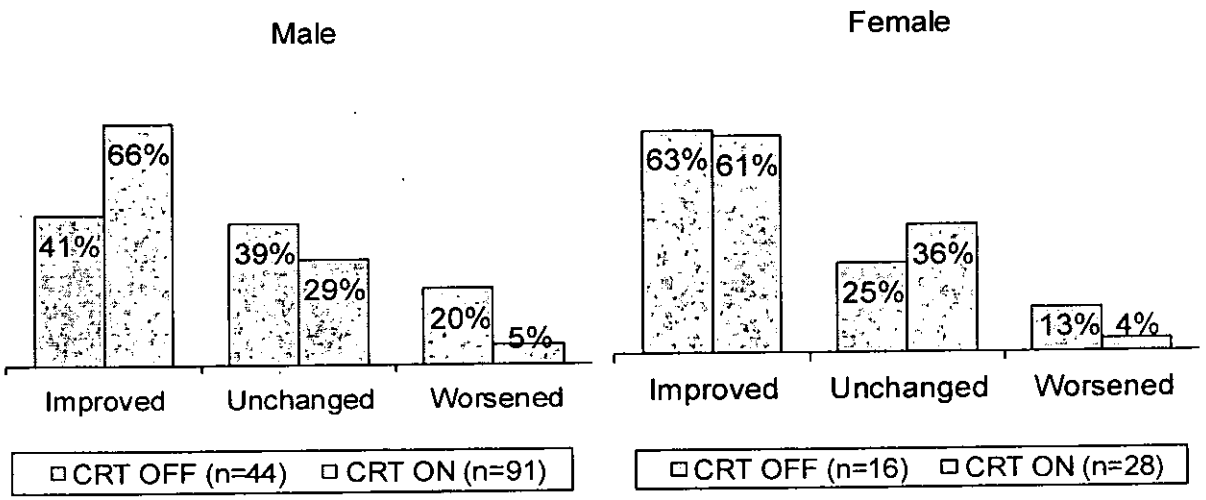
The primary endpoint results by gender are presented in Figure 16. There is no evidence of differences in worsened Clinical Composite Response between males and females (p=0.90).

Figure 16: REVERSE Clinical Composite Response at 12 Months by Gender – Full Cohort



Looking at the expanded indication population in Figure 17, again there is no significant difference in worsened Clinical Composite Response between males and females (p=0.92).

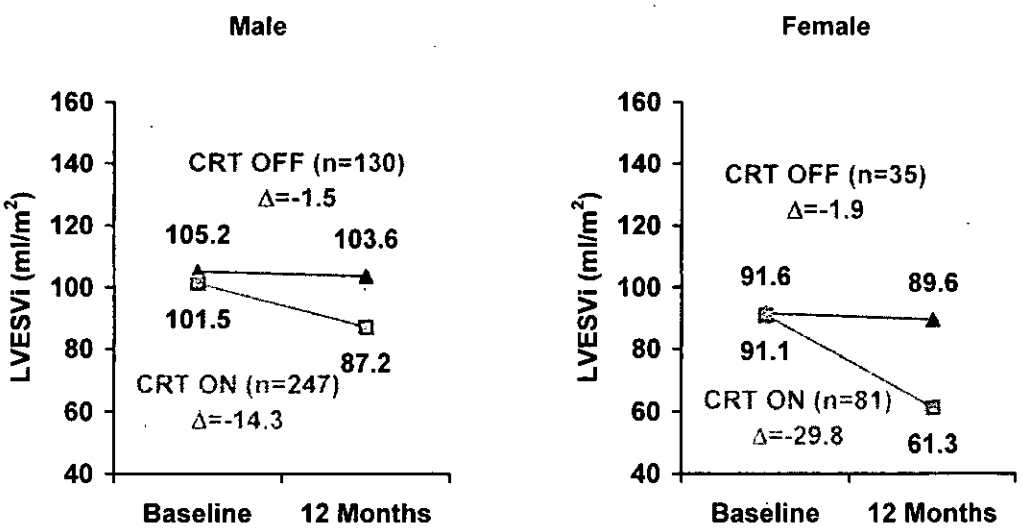
Figure 17: REVERSE Clinical Composite Response at 12 Months by Gender - Expanded Indication Population



Key Secondary Endpoint

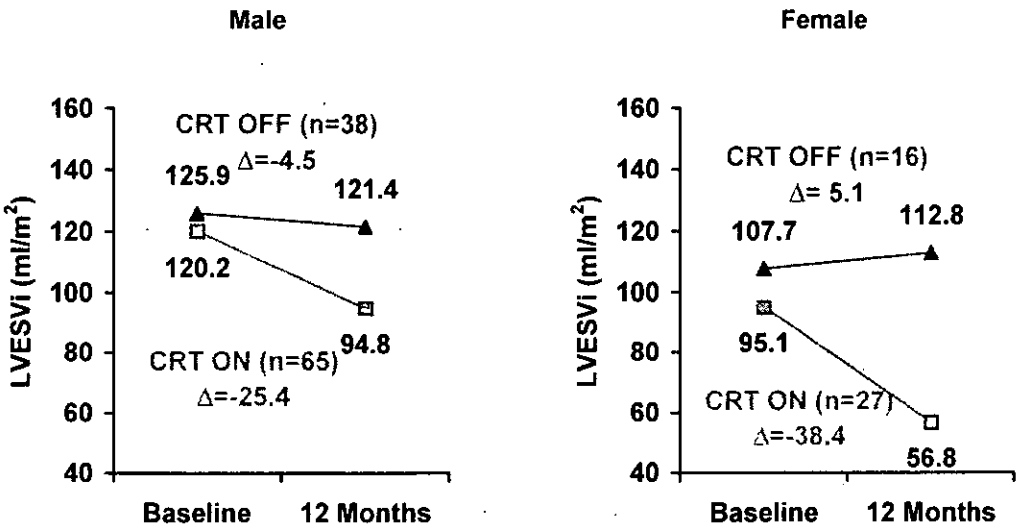
Change in left ventricular end systolic volume indexed (LVESVi) from baseline to 12 months was a secondary endpoint in REVERSE. Figure 18 shows the results for males and females. Though both improved their LVESVi with CRT, females showed more of an improvement than males (p=0.02).

Figure 18: REVERSE LVESVi Change at 12 Months by Gender - Full Cohort



Similar results are seen in Figure 19 in the expanded indication population where females again tended to have a larger reduction in LVESVi with CRT than males (p=0.05).

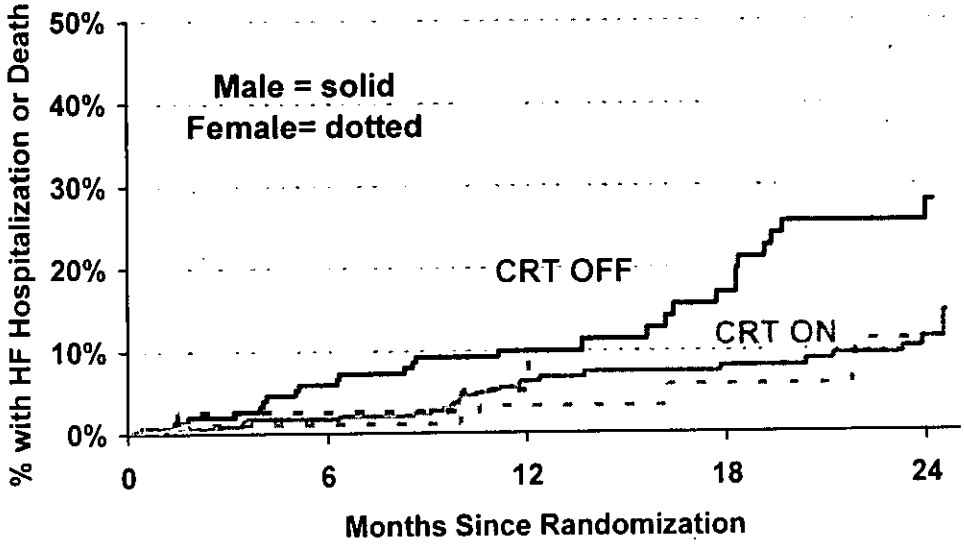
Figure 19: REVERSE LVESVi Change at 12 Months by Gender - Expanded Indication Population



Additional Analyses

Results by male and female for time to first heart failure hospitalization or all-cause death can be seen in Figure 20. There is no evidence of differences in CRT OFF vs. CRT ON results between males and females (p=0.48). Both males and females showed improvement with CRT. Males had a hazard ratio of 0.46 (54% reduction in HF hospitalization or death), while females had a 0.77 hazard ratio.

Figure 20: REVERSE Time to First HF Hospitalization or All-cause Death by Gender - Full Cohort



NR male	152	143	99	59	29
	327	321	218	133	69
NR female	39	38	27	11	10
	92	90	64	36	18

A similar figure could not be done for the expanded indication population because the female subgroup was too small (44 patients with 4 HF hospitalizations or deaths). There is no indication in these limited data that there is a difference in CRT effectiveness in reducing HF hospitalizations or deaths between males and females (p=0.74).

RAFT Clinical Study

A. Study Design

Overview

The study was a prospective, randomized, double-blind, multi-center, global post-market clinical study conducted in Canada, Europe, Turkey and Australia. The study was designed to determine whether biventricular pacing with an ICD (CRT-D) plus optimal medical therapy (OMT) reduces total mortality and heart failure hospitalizations as compared to ICD plus OMT in subjects with mild to moderate

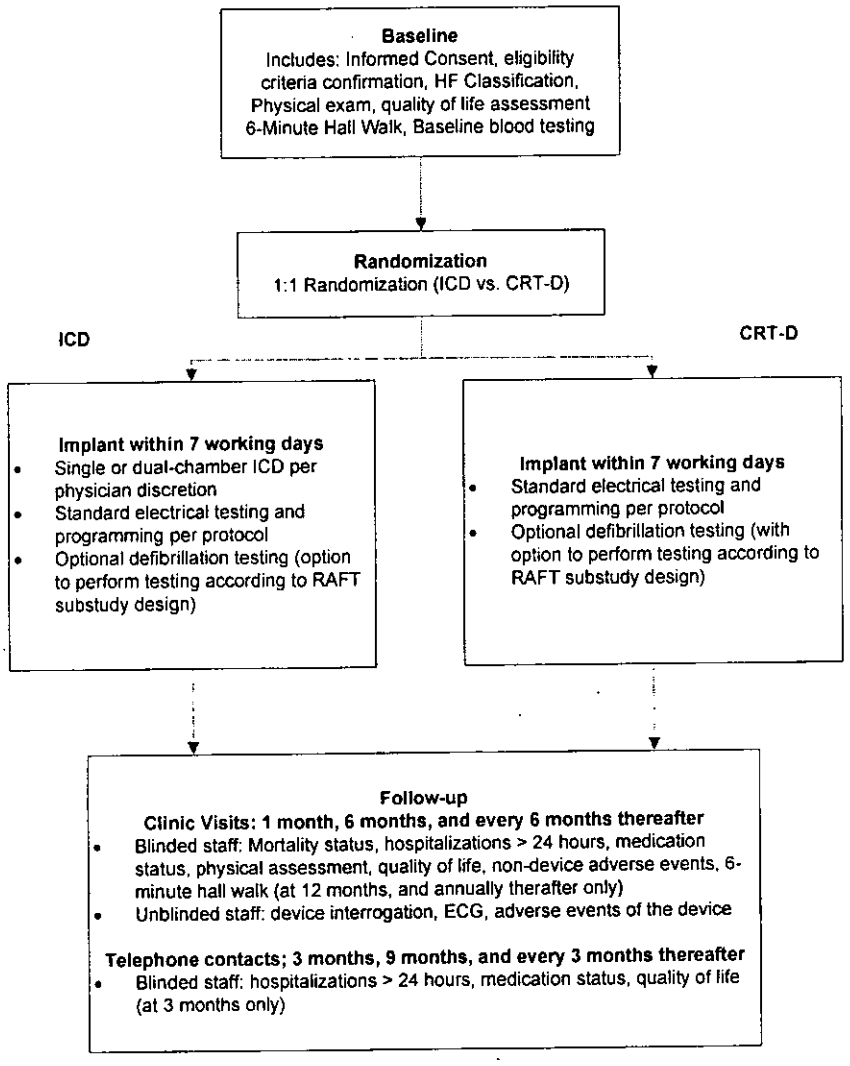
heart failure (New York Heart Association (NYHA) Functional Class II and III), ventricular dyssynchrony (intrinsic QRS $\geq$ 120 ms), and reduced systolic left ventricular ejection fraction (EF $\leq$ 30%). The University of Ottawa Heart Institute functioned as the Coordinating Center and overall sponsor for the study.

Subjects were enrolled between January 13, 2003 and February 27, 2009. The RAFT data included in this PMA supplement occurred on or before September 15, 2010. Updates to the database were allowed until the final database freeze on November 12, 2010. A total of 1798 subjects were enrolled and randomized at 34 investigational sites.

Eligible subjects who signed informed consent were randomized in a 1:1 fashion to either CRT-D or ICD arms. Subjects received commercially available Medtronic devices and commercially available leads. Subjects were followed for a minimum of 18 months and remained blinded for the duration of the study.

The study schematic for visits is shown in Figure 21.

Figure 21: RAFT Study Schematic



Statistical Methods

The primary objective of this study was to determine if the addition of CRT to optimal medical therapy and ICD is effective in reducing morbidity and mortality in patients with poor LV function, wide QRS and heart failure symptoms.

The log-rank test was used to compare the time to first HF hospitalization or all-cause death between the CRT-D group and the ICD group.

All statistical analyses were done using frequentist methods.

Two (2) interim analyses were planned and executed: the first analysis when 33% of subjects enrolled had been followed for 18 months and a second analysis when 66% of subjects enrolled had been followed for 18 months. A final analysis was performed at the conclusion of the trial. An O'Brien-Fleming alpha spending function was used to adjust the sample size for interim analysis.

In addition, after all subjects were recruited into the study, the overall composite event rate was calculated at 6 months and 12 months to determine if the planned follow-up period of 18 months could be reduced. For this assessment, the procedures outlined by Wittes[3] and Betensky[4] were followed and no adjustment was needed for the sample size. At each interim analysis, the DSMB recommended continuation of the study.

When the RAFT study was initiated, the composite event rate of total mortality and HF hospitalization was estimated to be 25% per year. This was based on a total mortality rate of 11% and an annual HF hospitalization rate of 20 - 25 % in the control arm. These estimates were based on an annual mortality rate of 11.2% in the MADIT II subgroup with QRS > 120 ms,[5] and a 25 - 30% HF hospitalization rate in the MIRACLE ICD[6] and CONTAK-CD trials.[7] MADIT II, MIRACLE ICD, and CONTAK CD are all previously conducted trials that are relevant to the RAFT study design. Some overlap of these two (2) endpoints was expected; therefore a conservative estimate of 25% per year primary endpoint event rate was made.

In order to detect a 20% relative risk reduction (i.e. an absolute annual reduction of 5%) in the primary endpoint under the experimental group (CRT-D), at alpha = 0.05 (two-sided) and 90% power, a sample size of 1500 subjects would be needed (750 in the control group and 750 in the experimental group). This calculation assumed an exponential survival with all subjects followed to the primary endpoint or termination of the study. This calculation allowed for a 5% inability to implant the LV lead (this was based on the most recent data of 96% implant success rate in a world-wide registry) and allowed for 3% of crossover from control group (ICD) to experimental group (CRT-D). This treatment comparison was based on the log-rank test.

Initially, RAFT allowed enrollment of both NYHA Class II and III subjects. In 2005, the CARE-HF trial results were published[8], which showed that patients with NYHA Class III or IV, reduced LVEF, and ventricular dyssynchrony had significant morbidity and mortality benefits associated with CRT. This led to published guidelines (ACC/AHA; HFSA; Canadian Cardiovascular Society/ESC) recommending CRT pacing for that patient population.[9,10,11] Because of this, the RAFT study design was updated (protocol version 4, dated February 28, 2006) to enroll only NYHA Class II subjects thereafter. Therefore, the composite endpoint event rate was decreased. The consensus among the RAFT investigators was to select an event rate of 12.6% for the ICD-only study group.

With the decision to enroll only NYHA Class II subjects, statistical assumptions were re-assessed. Past CRT and ICD trials were reviewed for the selection of power and relative risk reduction (RRR) for the minimal clinically important difference (MCID). In particular, studies with a primary endpoint that included mortality and/or heart failure hospitalization were assessed. As the choice for power usually varied between 80% and 90%, an 85% power was selected. The prior studies' RRR usually varied between 25% and 40%, and after discussion with the RAFT investigators, the RRR was adjusted from 20% to 25% for the composite endpoint.

Based on the 25% RRR and the 12.6% event rate for ICD-only, the event rate for the ICD/CRT group was forecasted to be 9.06%. The event rate for the overall group was revised to 11%.

All of the above changes in assumptions resulted in a new overall study sample size of 1800 subjects to achieve 85% power.

Because the endpoints of the study were analyzed using standard Kaplan-Meier survival methods, missing data was not an issue.

Study Oversight
An Event Committee was established to assess, review and classify all study exits (including deaths) and hospitalizations greater than 24 hours during the clinical study. An HF hospitalization was defined as an admission to a healthcare facility lasting more than 24 hours with symptoms of congestive heart failure and subsequent treatment for heart failure that was adjudicated by the Event Committee as heart failure exacerbation. The committee members were blinded to the randomization assignment and site of the subjects.

A Data Safety and Monitoring Board (DSMB) was appointed to assess treatment effects during the trial and provide advice about the conduct of the trial and integrity of the data, so as to protect the validity and scientific credibility of the trial. The DSMB reviewed non-blinded cumulative study data semi-annually, with a focus on safety issues and study conduct. The committee also reviewed data resulting from each of the interim analyses. The committee recommended trial continuation at each of their meetings.

Control Group
The control group received an ICD implant, while the experimental group received a CRT-D. Both groups received OMT. Subjects in both groups, along with the heart failure clinicians, were blinded to the device implanted.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the RAFT study was limited to patients who met the following key inclusion criteria:

   - NYHA Class II or III [revised to NYHA Class II only during later versions of the protocol]
   - LVEF $\leq$ 30% by MUGA/Catheterization OR LVEF $\leq$ 30% and LV end diastolic dimension $\geq$ 60 mm (by echocardiogram) within 6 months prior to randomization
   - Intrinsic QRS Complex Width $\geq$ 130 ms [revised to $\geq$ 120 ms during later versions of the protocol] OR paced QRS measurement $\geq$ 200 ms [added in latter versions of the protocol]
   - ICD indication for primary or secondary prevention
   - Optimal heart failure pharmacological therapy

- Normal Sinus Rhythm or Chronic persistent Atrial Tachyarrhythmia with resting Ventricular Heart Rate ≤ 60 bpm and 6 Minute Hall Walk Ventricular Heart Rate of ≤ 90 bpm OR Chronic persistent Atrial Tachyarrhythmia with resting Ventricular Heart Rate > 60 bpm and 6 Minute Hall Walk Ventricular Heart Rate of > 90 bpm and booked for Atrio-Ventricular Junction Ablation

Patients were not permitted to enroll in the RAFT study if they met any of the following key exclusion criteria:

- Intravenous inotropic agent in the last four days
- Patients with an acute coronary syndrome including MI can be included if the patient has had a previous MI with LV dysfunction (LVEF ≤ 30%)
- In-hospital patients who have acute cardiac or non-cardiac illness that requires intensive care
- Restrictive, hypertrophic or reversible form of cardiomyopathy
- Patients with an existing ICD (Patients with an existing pacemaker may be included if the patients satisfies all other inclusion/exclusion criteria)
- Coronary revascularization (Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI)) < 1 month if previously determined LVEF > 30%
- Patients with a more recent revascularization can be included if a previous determined LVEF was ≤ 30%

All subjects were required to receive optimal medical therapy for 6 weeks prior to enrollment. This was defined to be:

- ACE Inhibitor/ARB: All patients were to receive ACE inhibitor whenever possible, limited by symptomatic hypotension, renal dysfunction, cough, allergic reaction, or significant other side effect. A target dosage of enalapril 10 – 20 mg bid (or equivalent ACE inhibitor and dosage) was recommended. For patients unable to tolerate ACE inhibitor, an ARB or a hydralazine/nitrate combination was expected.
- Beta-blocker: All patients were to receive a beta-blocker whenever possible, limited by symptomatic bradycardia, allergic reaction, or significant side effect. A target dosage of metoprolol 75 mg BID, carvedilol 25 mg BID, or bisoprolol 10 mg OD was recommended unless limited by symptomatic bradycardia or hypotension, pulmonary wheeze, allergic reaction, or significant other side effect.
- Digoxin: Digoxin was allowed at the discretion of the treating physician.
- Nitrates: Any formulation of nitrates could be used for heart failure symptom control.
- Diuretic: Diuretics could be added or reduced according to patient's symptoms.
- Amiodarone: Amiodarone was allowed for the treatment of symptomatic atrial arrhythmias. Amiodarone was not to be started for asymptomatic or minimally symptomatic PVC or non-sustained VT.

- Other anti-arrhythmic medications: Amiodarone was expected to be the drug of choice if anti-arrhythmic drug is necessary. In the event that a patient required an anti-arrhythmic drug and was intolerant to or had significant side effects from amiodarone, another anti-arrhythmic drug could be chosen at the discretion of the treating physician.
- Anti-coagulant: Anticoagulants could be prescribed as clinically indicated.

Heart failure medication was allowed to be adjusted post-randomization during the study as indicated with the intention to provide optimal medical care for each patient. Up-titration of heart failure medications, especially beta-blockers and ACE inhibitors, was encouraged as this trial tested optimal therapy including device support for drug dosing. It was understood that drug imbalance would occur, but the result of the trial would be more applicable to the reality of heart failure patient care. Down-titration of heart failure medication was discouraged.

Amiodarone was allowed to be used for symptomatic ventricular arrhythmias developed after a subject's enrollment into the study or frequent ICD shocks due to atrial or ventricular arrhythmias.

2. Follow-up Schedule
Clinical assessments occurred at baseline, implant, 1 month, 6 months, and every 6 months thereafter until the last subject completed the 18-month follow-up visit. Clinical data were also collected for telephone contacts at 6-month intervals between clinic visits, hospitalizations greater than 24 hours, system modifications, and subject exit (including death). Implant procedure and system-related complications were recorded at all visits. Visit descriptions are summarized above in Figure 21.

3. Clinical Endpoints
The RAFT study did not have a pre-specified primary safety endpoint.

The primary effectiveness endpoint was a composite of all-cause mortality and hospitalization for heart failure. Hospitalization for heart failure (HF) was defined as an admission to a hospital with a diagnosis of worsening HF for greater than 24 hours.

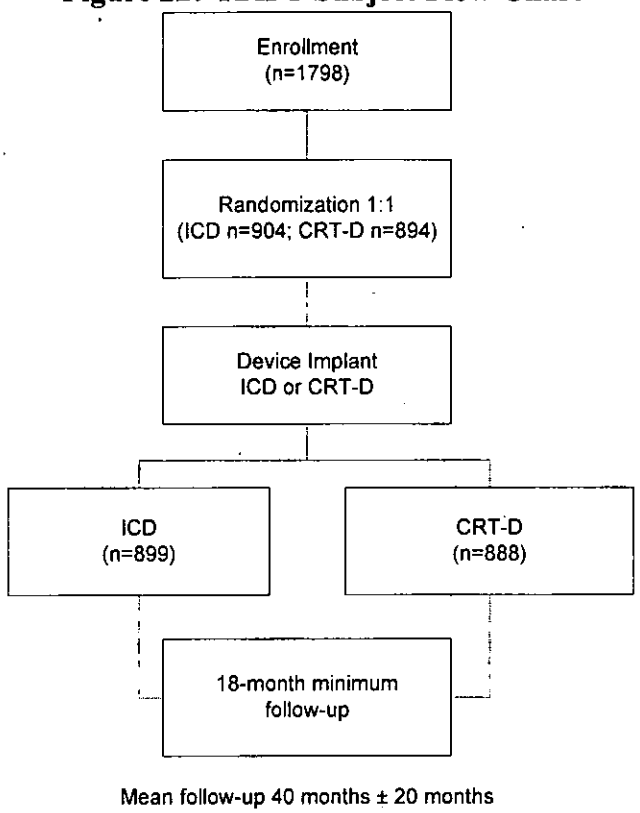
Success of the primary effectiveness endpoint was defined as a reduction in the composite endpoint of all-cause mortality and HF hospitalization for CRT-D subjects as compared to ICD subjects with the difference being statistically significant.

B. Accountability of PMA Cohort

At the time of the database lock, 1798 subjects had been enrolled and randomized in the study. All 1798 subjects were included in the study analyses.

The status of all subjects enrolled in the study is summarized in Figure 22.

Figure 22: RAFT Subject Flow Chart



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a heart failure study performed in the U.S.

Details on the baseline demographics for all 1798 subjects are provided below in **Table 12**. The subjects randomized in RAFT were predominantly male (82.9%). The average age at baseline was 66.1 years. Subjects had an average LVEF of 22.6%. The majority of subjects were NYHA Class II (80.0%).

Table 12: RAFT Baseline Demographics – Full Cohort

Subject Characteristic	ICD (n= 904)	CRT-D (n= 894)
Male	81% (732)	85% (758)
Age (years)	66.2 ± 9.4	66.1 ± 9.3
LVEF (%)	22.6 ± 5.1	22.6 ± 5.4
QRS Duration (ms)	158 ± 24	157 ± 24
QRS Morphology Type		
RBBB	10% (93)	8% (68)
LBBB	71% (643)	73% (652)
NIVCD	11% (101)	12% (106)
Ventricular paced	7% (67)	8% (68)
Ischemic	65% (587)	69% (614)
Diabetes	34.6% (313)	32.8% (293)
Hypertension	397 (43.9%)	402 (45.0%)
NYHA Classification		
Class II	81% (730)	79% (708)
Class III	19% (174)	21% (186)
Beta blocker	89% (805)	90% (808)
ACE-I/ARB	97% (878)	96% (859)
Diuretic	756 (84%)	85% (757)

For the expanded indication patient population, 850 (47%) RAFT subjects meet the labeling criteria. Baseline demographics for the expanded indication population from RAFT are presented in Table 13.

Table 13: RAFT Baseline Demographics - Expanded Indication Population

Subject Characteristic	ICD (n= 425)	CRT-D (n= 425)
Male	80% (338)	83% (354)
Age (years)	64.8 ± 9.1	65.0 ± 9.6
LVEF (%)	22.6 ± 5.2	22.4 ± 5.3
QRS duration (ms)	166 ± 22	164 ± 22
QRS Morphology Type		
RBBB	0% (0)	0% (0)
LBBB	100% (425)	100% (425)
NIVCD	0% (0)	0% (0)
Ventricular paced	0% (0)	0% (0)
Ischemic	56% (238)	62% (262)
Diabetes	32% (135)	30% (129)
Hypertension	44% (185)	47% (198)
NYHA Classification		
Class II	100% (425)	100% (425)
Class III	0% (0)	0% (0)
Beta blocker	90% (384)	93% (394)
ACE-I/ARB	98% (415)	96% (407)
Diuretics	81% (344)	81% (346)

D. Safety and Effectiveness Results

1. Safety Results

Procedure and system-related complications were collected at implant and each follow-up visit for the RAFT study. These complications were reviewed at DSMB meetings to ensure patient safety and adjudicated by a blinded Event Committee. No specific objective was pre-specified surrounding adverse events.

Adverse effects that occurred in the PMA clinical study:

A summary of all procedure or system-related complications occurring in the study is presented in Table 14, which is sorted in descending order based on the total number of events. Of the 1798 randomized subjects, 1787 had an attempted device implant and accrued 5974 years of follow-up (ICD: n=899, 2923 years; CRT-D: n=888, 3051 years). During the study, 894 procedure or system-related complications were reported in 583 subjects.

In the ICD group, 24.9% of the subjects had at least one procedure or system-related complication during the study, and 40.4% of the subjects in the CRT-D

group reported at least one. Much of the difference was due to expected battery depletion and subsequent device replacement in the CRT-D group. In the first 30 days post implant, 6.0% of the subjects in the ICD group had a procedure or system-related complication, compared to 11.7% of the subjects in the CRT-D group.

Table 14: RAFT Procedure or System-Related Complications

Procedure or System-related Complications During Follow-up Number of Events (Number of Subjects, % of Subjects with an Attempted Implant)						
	All subjects n = 1787 Years of follow-up = 5974.0		**ICD group n = 899 Years of follow-up = 2922.9**		**CRT-D group n = 888 Years of follow-up = 3051.1**	
Key Term	**# AEs**	**# AEs within 30 days of implant**	**# AEs**	**# AEs within 30 days of implant**	**# AEs**	**# AEs within 30 days of implant**
Expected battery depletion leading to PG change	219 (216, 12.1%)	0 (0, 0%)	28 (28, 3.1%)	0 (0, 0%)	191 (188, 21.2%)	0 (0, 0%)
Lead dislodgement – intervention	190 (160, 9.0%)	81 (77, 4.3%)	56 (49, 5.5%)	22 (21, 2.3%)	134 (111, 12.5%)	59 (56, 6.3%)
Upgrade to CRT-D	102 (102, 5.7%)	1 (1, 0.1%)	101 (101, 11.2%)	1 (1, 0.1%)	1 (1, 0.1%)*	0 (0, 0%)
Prophylactic lead replacement	61 (61, 3.4%)	1 (1, 0.1%)	27 (27, 3.0%)	0 (0, 0%)	34 (34, 3.8%)	1 (1, 0.1%)
Lead fracture	55 (53, 3.0%)	0 (0, 0%)	16 (16, 1.8%)	0 (0, 0%)	39 (37, 4.2%)	0 (0, 0%)
Pocket infection – intervention	45 (42, 2.4%)	8 (8, 0.4%)	18 (18, 2.0%)	4 (4, 0.4%)	27 (24, 2.7%)	4 (4, 0.5%)
Sensing/pacing issues	45 (43, 2.4%)	3 (3, 0.2%)	15 (15, 1.7%)	0 (0, 0%)	30 (28, 3.2%)	3 (3, 0.3%)
Premature battery depletion	43 (43, 2.4%)	0 (0, 0%)	16 (16, 1.8%)	0 (0, 0%)	27 (27, 3.0%)	0 (0, 0%)
Prophylactic pulse generator replacement	30 (30, 1.7%)	0 (0, 0%)	7 (7, 0.8%)	0 (0, 0%)	23 (23, 2.6%)	0 (0, 0%)
Pocket hematoma- intervention	25 (25, 1.4%)	20 (20, 1.1%)	11 (11, 1.2%)	9 (9, 1.0%)	14 (14, 1.6%)	11 (11, 1.2%)
Hemo/pneumothorax- intervention	20 (20, 1.1%)	18 (18, 1.0%)	8 (8, 0.9%)	8 (8, 0.9%)	12 (12, 1.4%)	10 (10, 1.1%)
CS dissection	14 (14, 0.8%)	13 (13, 0.7%)	1 (1, 0.1%)	0 (0, 0%)	13 (13, 1.5%)	13 (13, 1.5%)
Other - increase hospitalization	12 (12, 0.7%)	9 (9, 0.5%)	7 (7, 0.8%)	7 (7, 0.8%)	5 (5, 0.6%)	2 (2, 0.2%)
Loose set screw	11 (11, 0.6%)	6 (6, 0.3%)	6 (6, 0.7%)	3 (3, 0.3%)	5 (5, 0.6%)	3 (3, 0.3%)
Device pocket problems requiring revision	10 (10, 0.6%)	0 (0, 0%)	4 (4, 0.4%)	0 (0, 0%)	6 (6, 0.7%)	0 (0, 0%)
HF exacerbation - intervention IV meds and increase hospitalization	7 (7, 0.4%)	7 (7, 0.4%)	3 (3, 0.3%)	3 (3, 0.3%)	4 (4, 0.5%)	4 (4, 0.5%)
Cardiac perforation/pericarditis/tamponade – intervention	5 (5, 0.3%)	3 (3, 0.2%)	2 (2, 0.2%)	0 (0, 0%)	3 (3, 0.3%)	3 (3, 0.3%)
Total	**894 (583, 32.6%)**	**170 (158, 8.8%)**	**326 (224, 24.9%)**	**57 (54, 6.0%)**	**568 (359, 40.4%)**	**113 (104, 11.7%)**

* Subject 19007 had CRT-D explanted due to perforation of the right lung. A St. Jude CRT-D was subsequently implanted.

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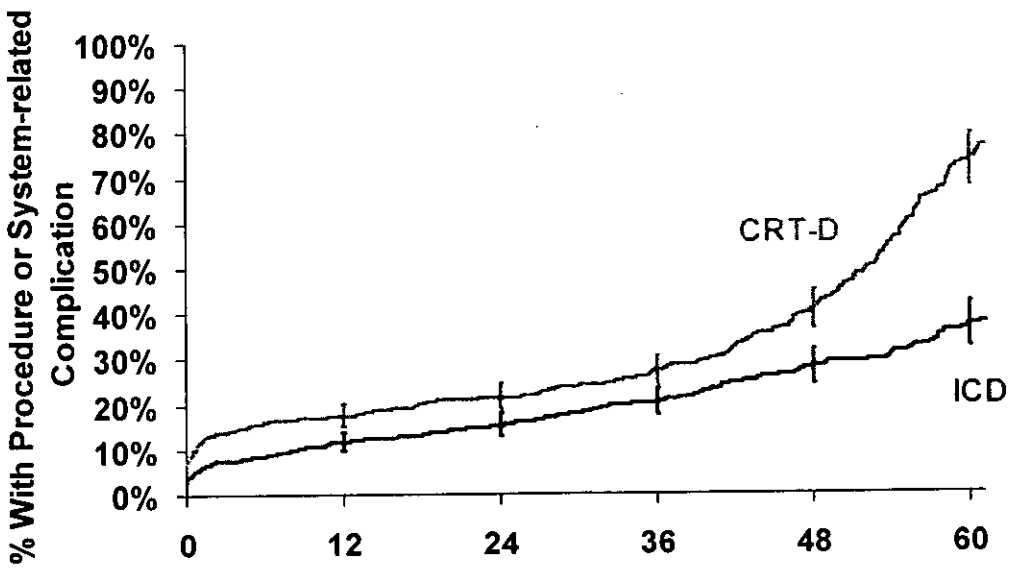
A Kaplan-Meier curve for the time to first procedure or system-related complication is shown in Figure 23. In the initial few months, the CRT-D group has a higher rate of procedure or system-related complications, but after about 3 months, the rate of these complications is similar between the ICD and CRT-D groups, as indicated by the similar slope of the curves. As expected, at about 48 months, the curve rises more rapidly in the CRT-D group due to subjects with a CRT-D device reaching end of battery life sooner than the subjects originally implanted with an ICD.

At 30 days, the procedure or system-related complication rate was 6.0% in the ICD group and 11.7% in the CRT-D group. At 12 months, the rate was 11.9% in the ICD group and 17.5% in the CRT-D group, and at 24 months the rate was 15.4% in the ICD group and 21.8% in the CRT-D group.

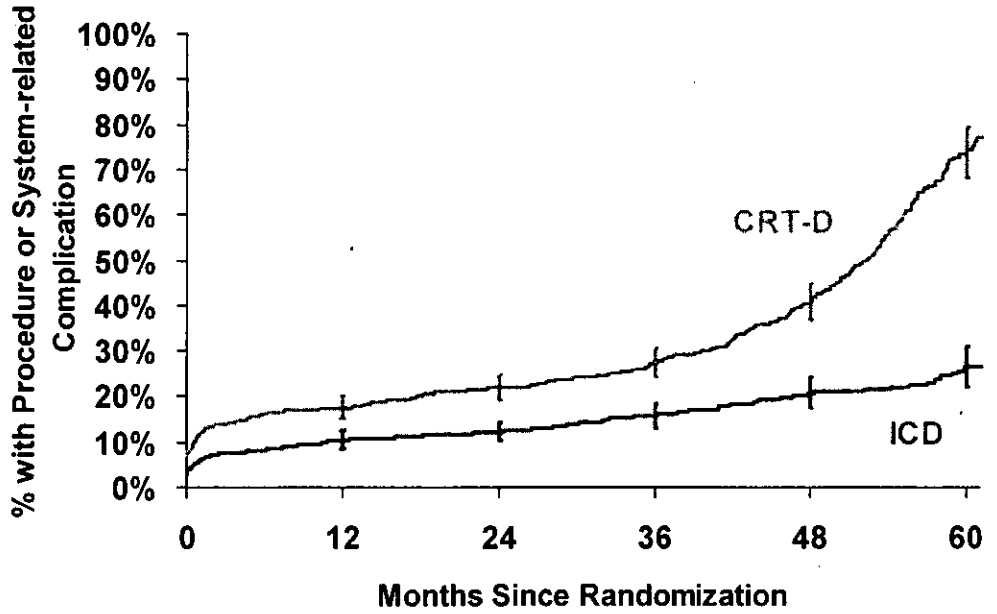
Figure 23: RAFT Time to First Procedure or System-Related Complication



Number	899	741	559	373	208	91
remaining	888	702	526	349	189	32

Figure 24 shows time to first procedure or system-related complication, but with CRT upgrades removed in the ICD arm. As anticipated, the number of complications in the ICD group is reduced.

Figure 24: RAFT – Time to First Procedure or System-Related Complication (excluding CRT-D upgrades in ICD group)



Number remaining	899	753	580	394	228	106
	888	702	526	349	189	32

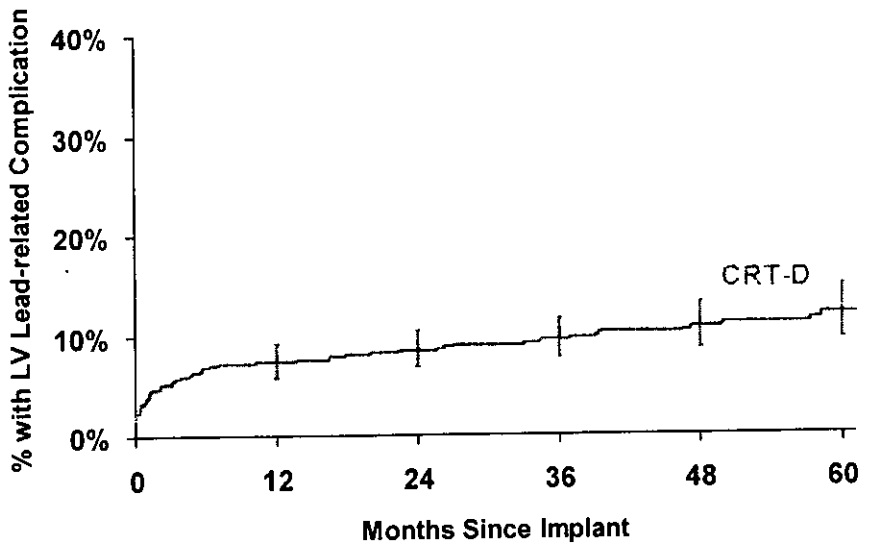
As all subjects in the RAFT study were indicated for an ICD, the incremental risk between the CRT-D group and the ICD group was the LV lead. There were 106 LV lead-related complications reported in the CRT-D group during the study as summarized in Table 15.

Table 15: RAFT LV Lead-Related Complications

Number of Events (Number of Subjects, % of Subjects with an Attempted Implant)		
	CRT-D group	
Key Term	# AEs	# AEs within 30 days of implant
Lead dislodgement - intervention	83 (72, 8.1%)	34 (31, 3.5%)
Sensing/pacing issues	15 (14, 1.6%)	3 (3, 0.3%)
Lead fracture	3 (2, 0.2%)	0 (0, 0%)
Prophylactic lead replacement	3 (3, 0.3%)	0 (0, 0%)
Loose set screw	2 (2, 0.2%)	1 (1, 0.1%)
Total	**106 (90, 10.1%)**	**38 (34, 3.8%)**

A Kaplan-Meier curve for the time to the first LV lead-related complication is shown in Figure 25. At 12 months, the LV lead-related complication rate in the CRT-D group was 7.4%. At 24 months, the rate in the CRT-D group was 9.6%. At 48 months, the rate was 10.8%.

Figure 25: RAFT Time to First LV Lead-Related Complication



Number remaining	888	784	615	440	291	136

Table 16 provides a summary of all deaths occurring during the course of the study.

Table 16: RAFT Cause of Death Summary

	ICD (n=904)	CRT-D (n=894)	Total (n=1798)
Non-cardiovascular	70 (30%)	54 (29%)	124 (29%)
Unexpected death presumed to be cardiovascular disease, occurring within 24 hrs of the onset of symptoms without confirmation of cardiovascular cause, and without clinical or post mortem evidence of etiology	25 (11%)	20 (11%)	45 (11%)
Myocardial Infarction: Death within 7 days of the onset of documented MI	4 (2%)	3 (2%)	7 (2%)
Congestive Heart Failure: Death due to clinical, radiological or post-mortem evidence of CHF, without clinical or postmortem evidence of other cause, such as ischemia, infection, dysrhythmia	95 (40%)	81 (44%)	176 (42%)
Post cardiovascular intervention: Death associated with the intervention: within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization/angioplasty	1 (<1%)	0 (0%)	1 (<1%)
Documented Arrhythmia: Death due to brady or tachyarrhythmias, not induced by an acute ischemic event	24 (10%)	23 (12%)	47 (11%)
Stroke: Death due to stroke occurring within 7 days of the signs and symptoms of stroke	13 (6%)	4 (2%)	17 (4%)
Other cardiovascular diseases: Death due to other vascular diseases such as pulmonary embolism, aortic aneurysm, etc.	0 (0%)	1 (1%)	1 (<1%)
Presumed cardiovascular death: Suspicion of CV death that does not fulfill other criteria	4 (2%)	0 (0%)	4 (1%)
Total	236 (100%)	186 (100%)	422 (100%)

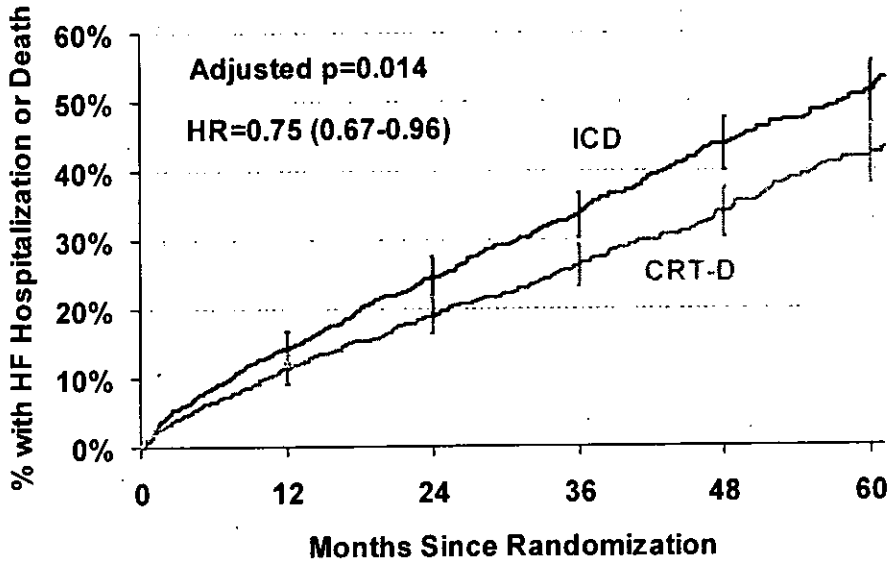
2. Effectiveness Results

The primary effectiveness endpoint based on the time to first heart failure hospitalization or all-cause death between the CRT-D and ICD groups was met and was based on the composite endpoint of all-cause mortality and heart failure (HF) hospitalization measured at the time of the database lock (after all subjects had completed the 18-month follow-up visit). Key effectiveness outcomes, including additional analyses supporting effectiveness, are presented below.

The primary endpoint for the study was time to first HF hospitalization or all-cause death. All hospitalizations greater than 24 hours were adjudicated by the blinded Adjudication Committee to be either heart failure related or not heart failure related. The time to the first HF hospitalization or all-cause death for all randomized subjects is shown in Figure 26. The primary outcome occurred in 364 of 904 subjects (40.3%) in the ICD group and 297 of 894 subjects (33.2%) in the CRT-D group. The hazard ratio was 0.75 in favor of CRT-D, which was

statistically significant (p adjusted for interim analysis=0.014). At 5 years, the observed rates were 51.3% in the ICD group and 42.4% in the CRT-D group.

Figure 26: RAFT Time to First HF Hospitalization or All-cause Death – Full Cohort

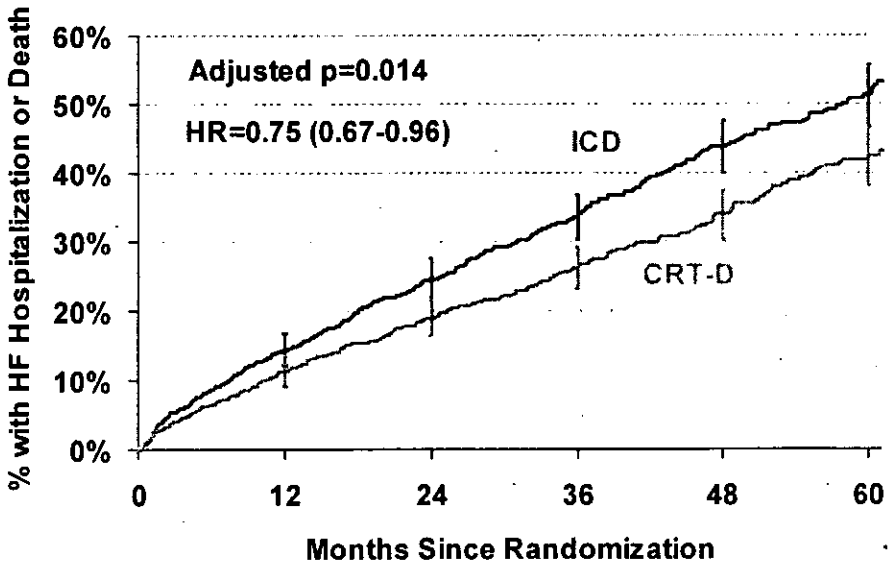


Number remaining	904	770	572	384	214	101
	894	790	615	429	278	130

A pre-specified subgroup analysis of NYHA Class II subjects was also performed. The time to first HF hospitalization or all-cause death for the 1438 NYHA Class II subjects only is shown in Figure 27. The primary outcome for the NYHA Class II subjects occurred in 253 of 730 subjects (34.7%) in the ICD group and 193 of 708 (27.3%) in the CRT-D group. The hazard ratio was 0.73 in favor of CRT-D, which was statistically significant (p=0.001). At 5 years, the rates were 48.1% in the ICD group and 40.0% in the CRT-D group.

statistically significant (p adjusted for interim analysis=0.014). At 5 years, the observed rates were 51.3% in the ICD group and 42.4% in the CRT-D group.

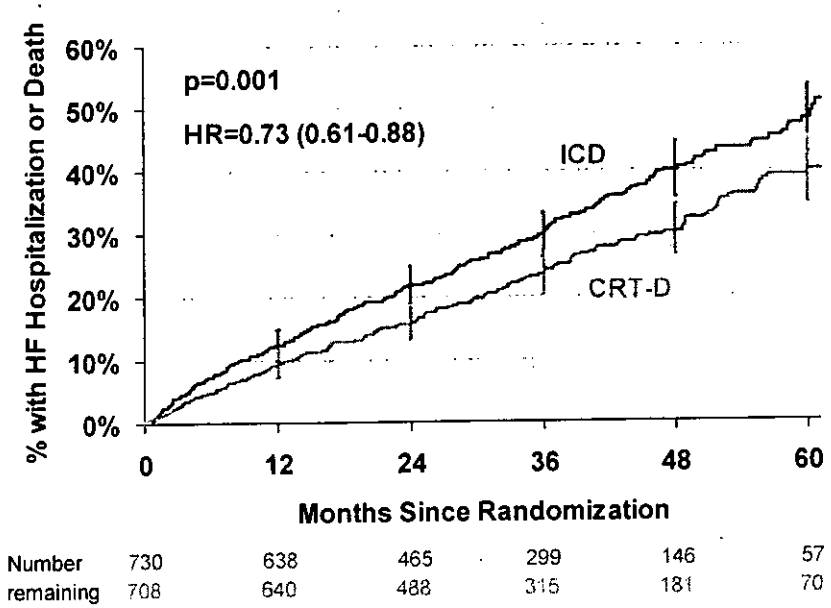
Figure 26: RAFT Time to First HF Hospitalization or All-cause Death – Full Cohort



Number remaining	904	770	572	384	214	101
	894	790	615	429	278	130

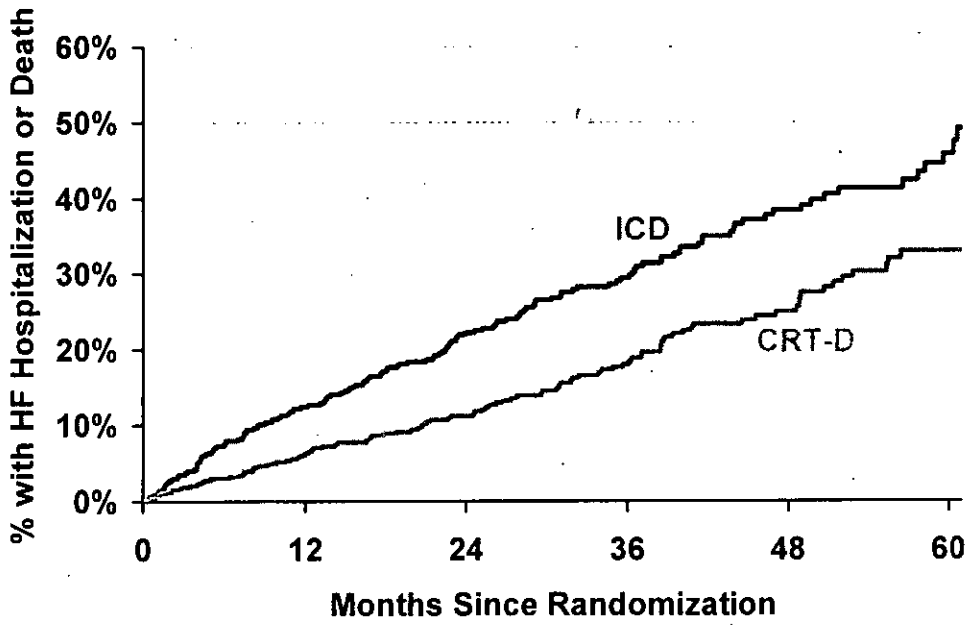
A pre-specified subgroup analysis of NYHA Class II subjects was also performed. The time to first HF hospitalization or all-cause death for the 1438 NYHA Class II subjects only is shown in Figure 27. The primary outcome for the NYHA Class II subjects occurred in 253 of 730 subjects (34.7%) in the ICD group and 193 of 708 (27.3%) in the CRT-D group. The hazard ratio was 0.73 in favor of CRT-D, which was statistically significant (p=0.001). At 5 years, the rates were 48.1% in the ICD group and 40.0% in the CRT-D group.

Figure 27: RAFT Time to First HF Hospitalization or All-cause Death - NYHA Class II Cohort



The primary endpoint was also analyzed for the expanded indication population (Figure 28). There was an observed 42% reduction in this endpoint with CRT-D. The estimated rate of HF hospitalization or all-cause death 4 years post-implant is 38.4% in the ICD group and 25.1% in the CRT-D group.

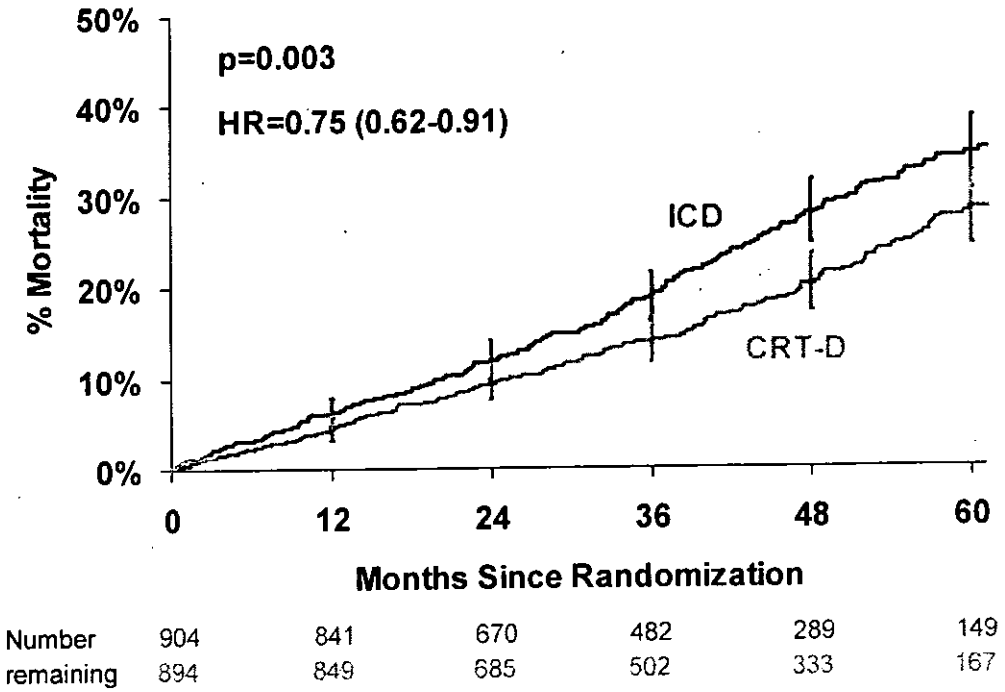
Figure 28: RAFT Time to First HF Hospitalization or All-cause Death – Expanded Indication Population



Number	425	372	269	176	89	35
remaining	425	399	312	207	122	47

Total mortality was analyzed as a secondary objective for the study. The time to all-cause death for all randomized subjects is shown in Figure 29. During the study, 236 of 904 (26.1%) of ICD subjects died and 186 of 894 (20.8%) of CRT-D subjects died. The hazard ratio was 0.75 in favor of CRT-D, which was statistically significant (p=0.003). At 5 years, the mortality rates were 34.6% in the ICD group and 28.6% in the CRT-D group.

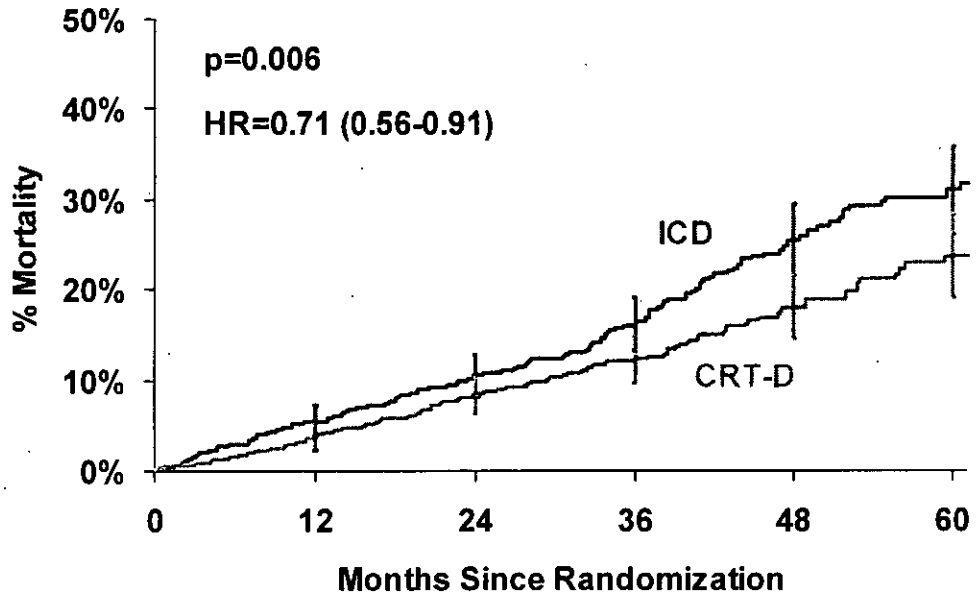
Figure 29: RAFT Mortality – Full Cohort



Number	904	841	670	482	289	149
remaining	894	849	685	502	333	167

A pre-specified subgroup analysis of NYHA Class II subjects was also performed. The time to all-cause death for the NYHA Class II subjects only is shown in Figure 30. Of the 730 NYHA Class II subjects in the ICD group, 154 (21.1%) of them died, while in the CRT-D group, 110 of 708 (15.5%) died. The hazard ratio was 0.71 in favor of CRT-D. These differences were statistically significant (p=0.006). At 5 years, the mortality rates were 31.0% in the NYHA Class II ICD group, and 23.7% in the NYHA Class II CRT-D group.

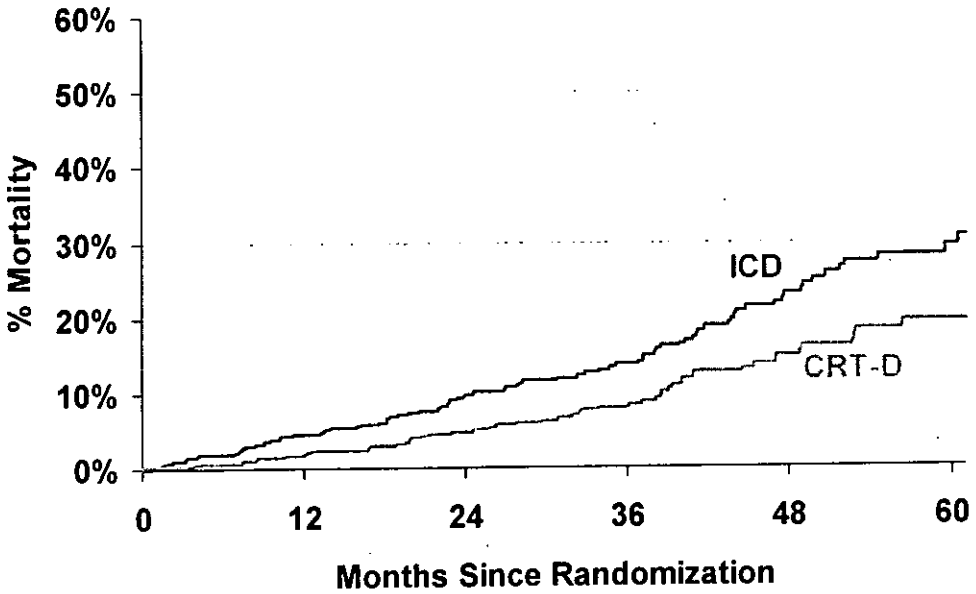
Figure 30: RAFT Mortality - NYHA Class II Cohort



Number	730	687	533	366	189	83
remaining	708	679	530	361	206	89

Total mortality was also analyzed for the expanded indication population (Figure 31). There was an observed 42% reduction in death with CRT-D. The estimated mortality rate 4 years post-implant is 23.2% in the ICD group and 14.9% in the CRT-D group.

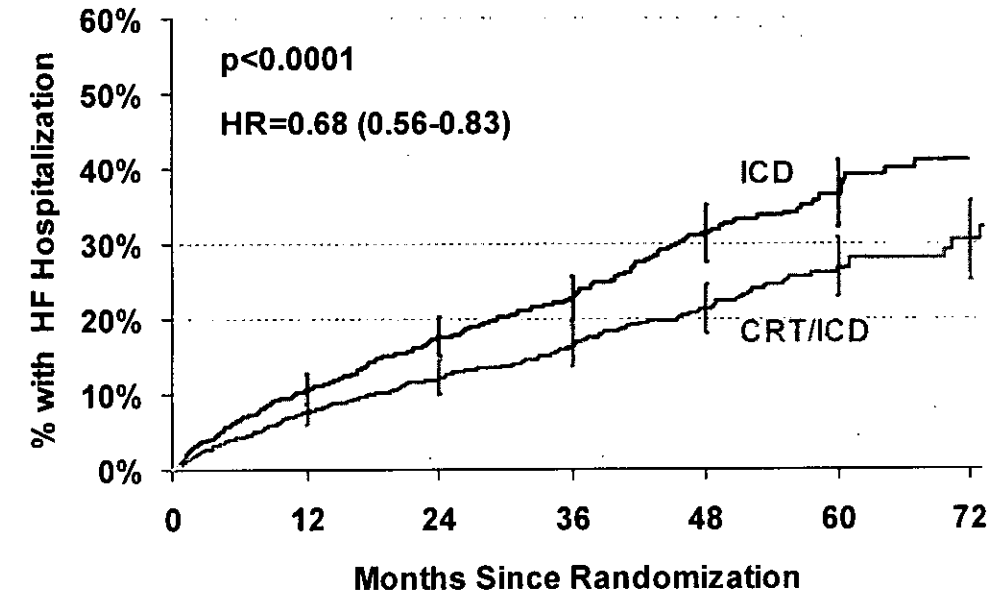
Figure 31: RAFT Mortality - Expanded Indication Population



Number	425	405	315	224	117	52
remaining	425	418	333	232	135	55

Additionally, time to first HF hospitalization was analyzed as a secondary endpoint for the study. The time to first HF hospitalization for all randomized subjects is shown in as shown in Figure 32. In the full cohort, 410 subjects were hospitalized for HF at least once (22.8%) over the course of the study. Hospitalization for HF occurred in 236 of 904 subjects (26.1%) in the ICD group and 174 of 894 (19.5%) in the CRT-D group. The hazard ratio was 0.68 in favor of CRT-D ($p<0.0001$). At 5 years, the HF hospitalization rates were 36.6% in the ICD group and 26.8% in the CRT-D group.

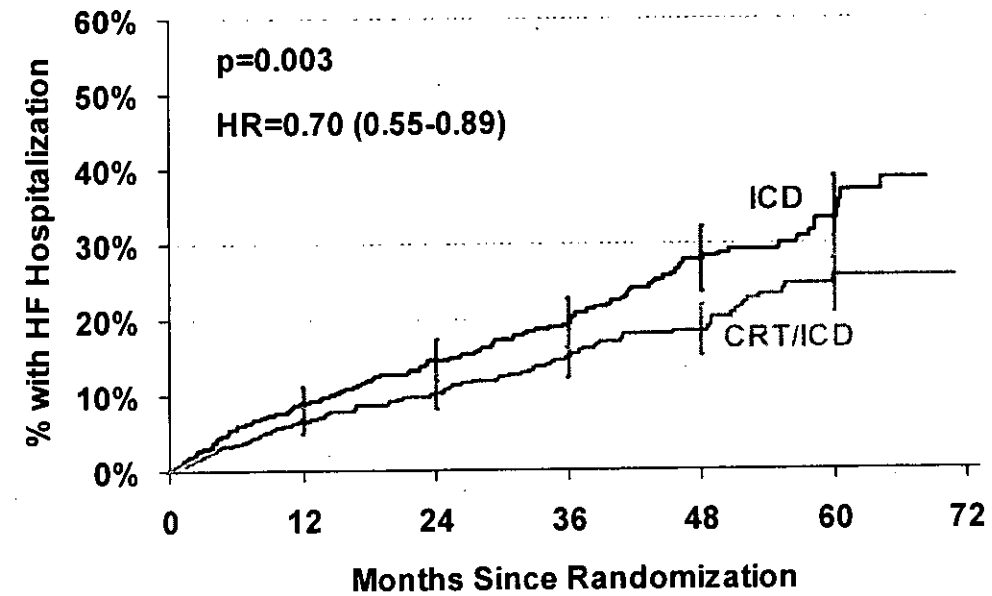
Figure 32: RAFT Time to First HF Hospitalization – Full Cohort



Number	904	770	572	384	214	101	19
remaining	894	790	615	429	278	130	41

A pre-specified subgroup analysis of NYHA Class II subjects was also performed. The time to first HF hospitalization for the NYHA Class II subjects only is shown in Figure 33. Of the 1438 NYHA Class II subjects, 274 experienced at least one heart failure hospitalization (19.1%). Hospitalization for heart failure occurred in 159 of 730 subjects (21.8%) in the ICD group and 115 of 708 (16.2%) in the CRT-D group. The hazard ratio was 0.70 in favor of CRT-D (p=0.003). At 5 years, the HF hospitalization rates were 33.3% in the NYHA Class II ICD group and 25.7% in the NYHA Class II CRT-D group.

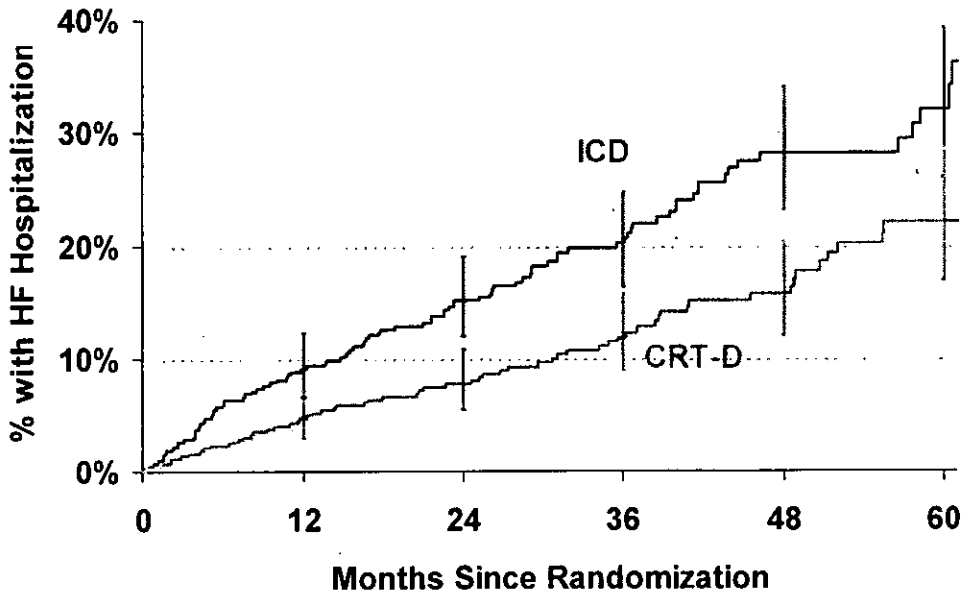
Figure 33: RAFT Time to First HF Hospitalization – NYHA Class II Cohort



Number	730	638	465	299	146	57	6
remaining	708	640	488	315	181	70	15

The time to first HF hospitalization was also analyzed for the expanded indication population (Figure 34). As with the full and NYHA Class II cohorts, a reduction in the risk of HF hospitalization was observed with CRT-D.

Figure 34: RAFT Time to First HF Hospitalization – Expanded Indication Population (post-hoc analysis)



Number	425	372	269	176	89	35
remaining	425	399	312	207	122	47

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: age, gender, NYHA Class, underlying heart disease type, QRS duration, LVEF, QRS morphology, atrial rhythm, diabetes, hypertension, and estimated glomerular filtration rate (eGFR).

Subgroup analyses performed for the RAFT NYHA Class II cohort for time to first HF hospitalization or all-cause death and total mortality are summarized below in Figure 35 and Figure 37. Lines represent 95% confidence intervals, which should be interpreted with the understanding that no subgroup was powered to see a difference between ICD and CRT-D. In addition, post-hoc subgroup analyses of QRS duration evaluated as a continuous variable, along with categorical analysis in groups of 10 ms (120-129, 130-139, etc.) are presented in Figure 36 and Figure 38.

Figure 35: RAFT Time to First HF Hospitalization or All-cause Death Subgroup Analysis - NYHA Class II Cohort (post-hoc analysis)

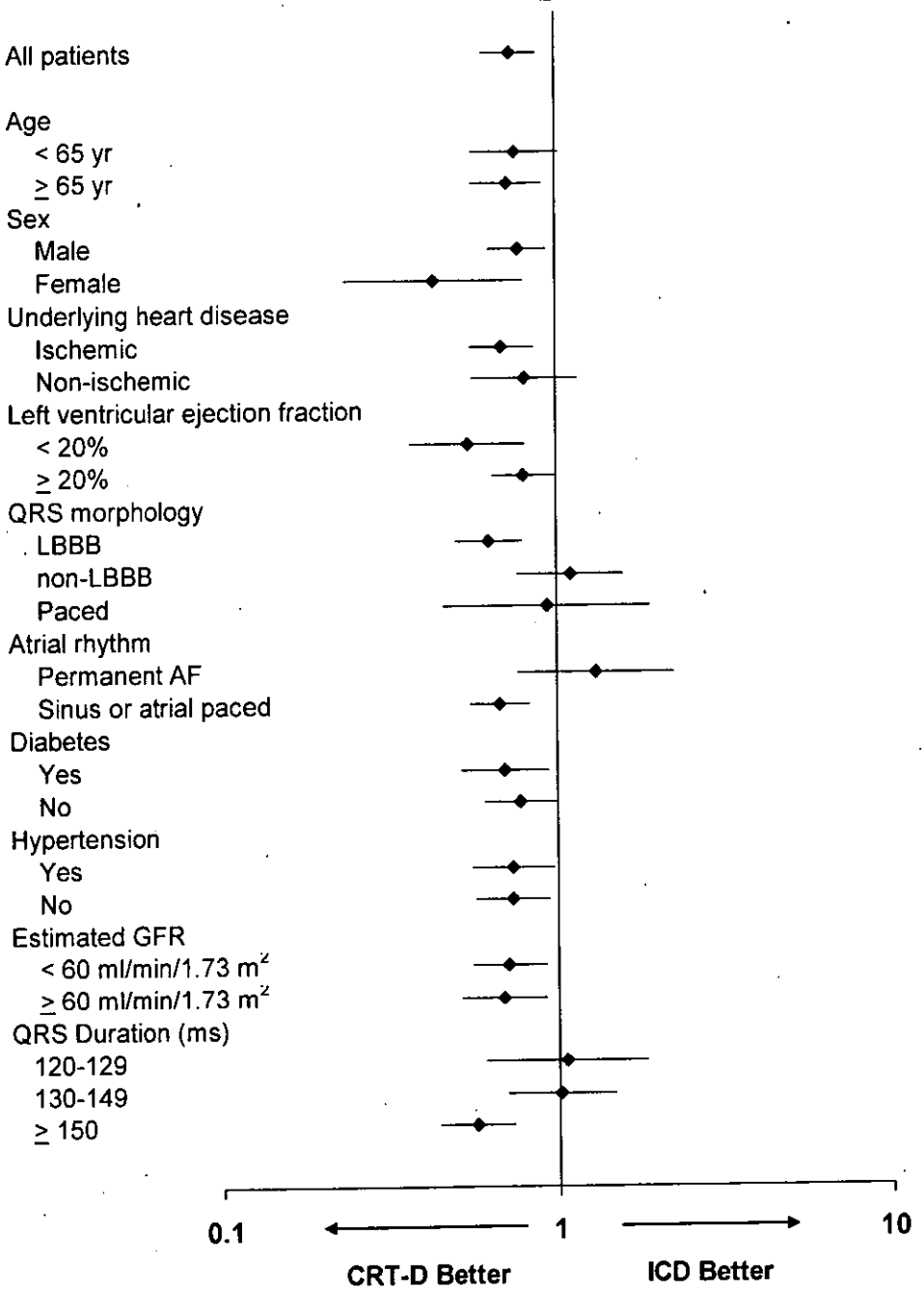


Figure 36: RAFT Time to First HF Hospitalization or All-Cause Death Subgroup Analysis: QRS Duration Hazard Ratio - NYHA Class II Cohort (post-hoc analysis)

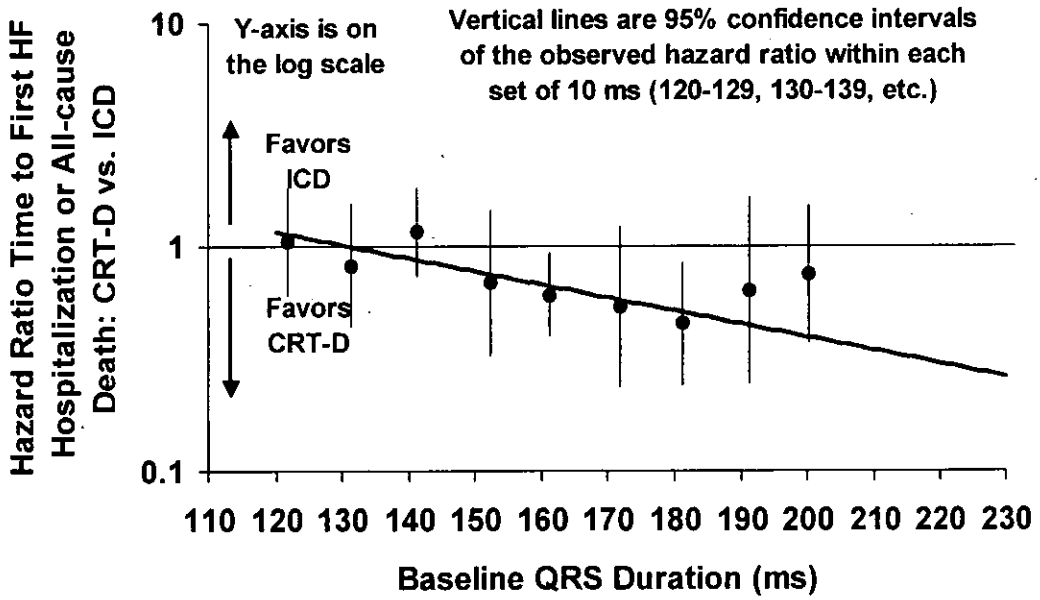


Figure 37: RAFT Mortality Subgroup Analysis - NYHA Class II Cohort (post-hoc analysis)

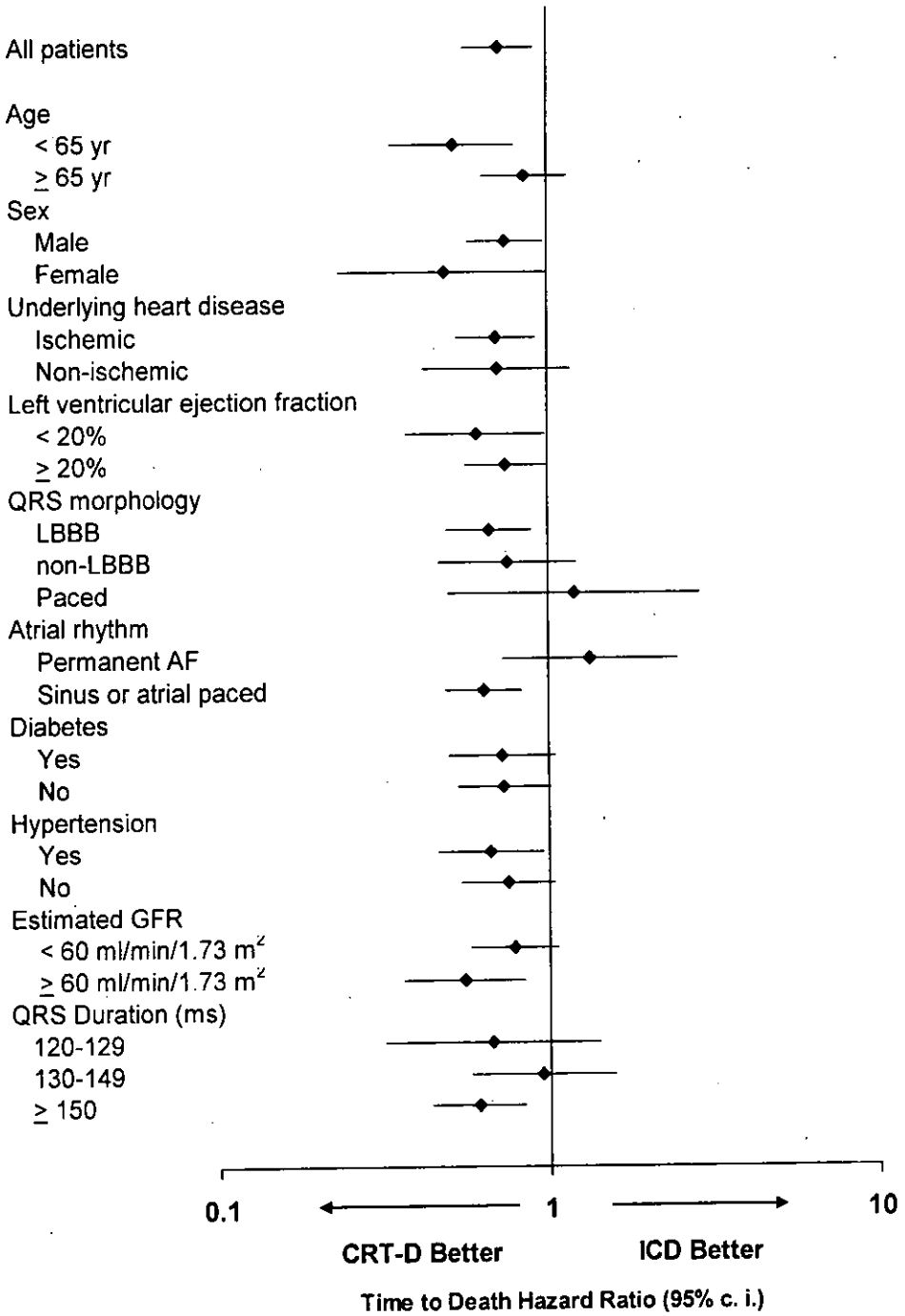
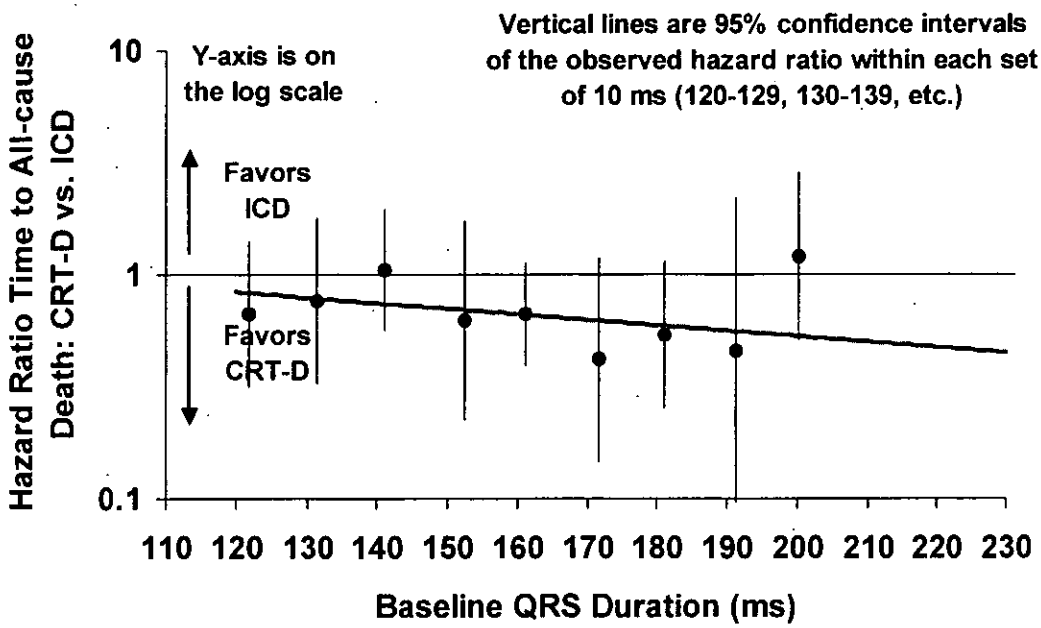


Figure 38: RAFT Mortality Subgroup Analysis: QRS Duration Hazard Ratio - NYHA Class II Cohort (post-hoc analysis)



Subgroup analyses for time to first HF hospitalization or death as well as for total mortality were also performed for the expanded indication population, as summarized in Figure 39 and Figure 40. Lines represent 95% confidence intervals, which should be interpreted with the understanding that no subgroup was powered to see a difference between ICD and CRT-D.

Figure 39: RAFT Time to First HF Hospitalization or All-cause Death Subgroup Analysis - Expanded Indication Population (post-hoc analysis)

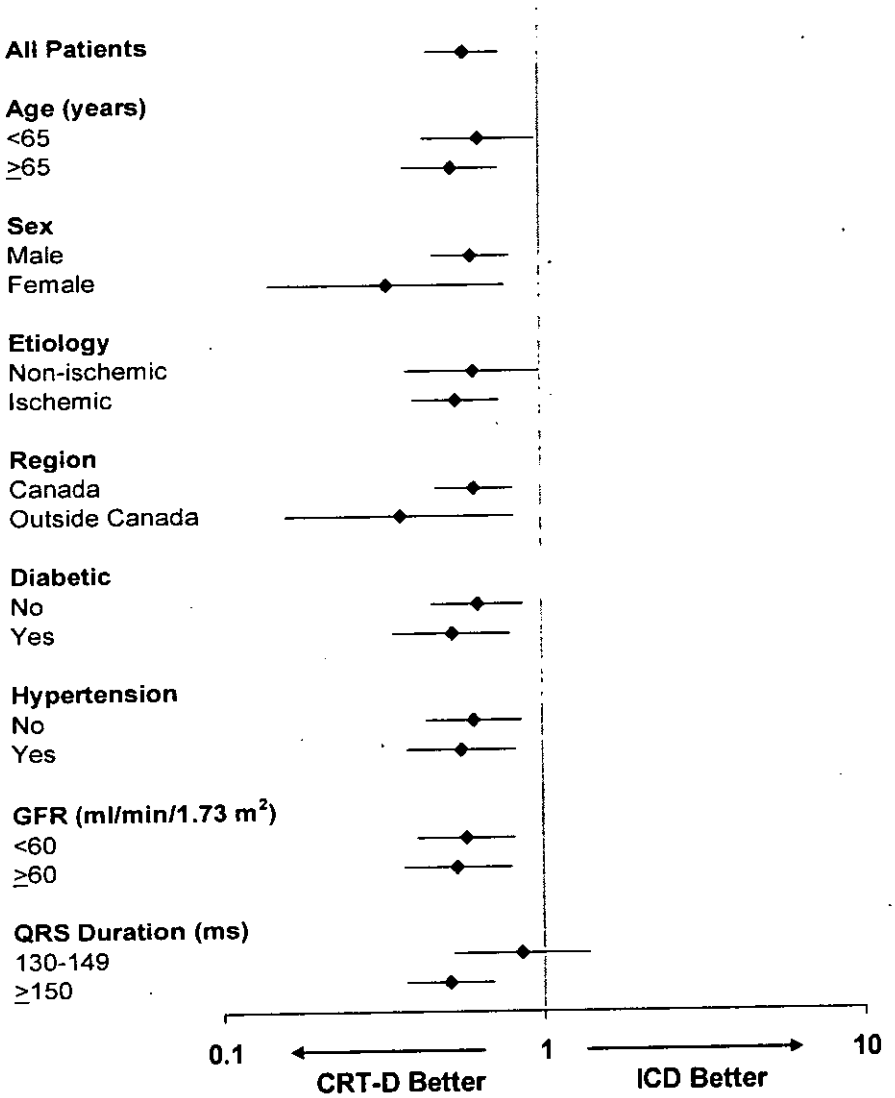
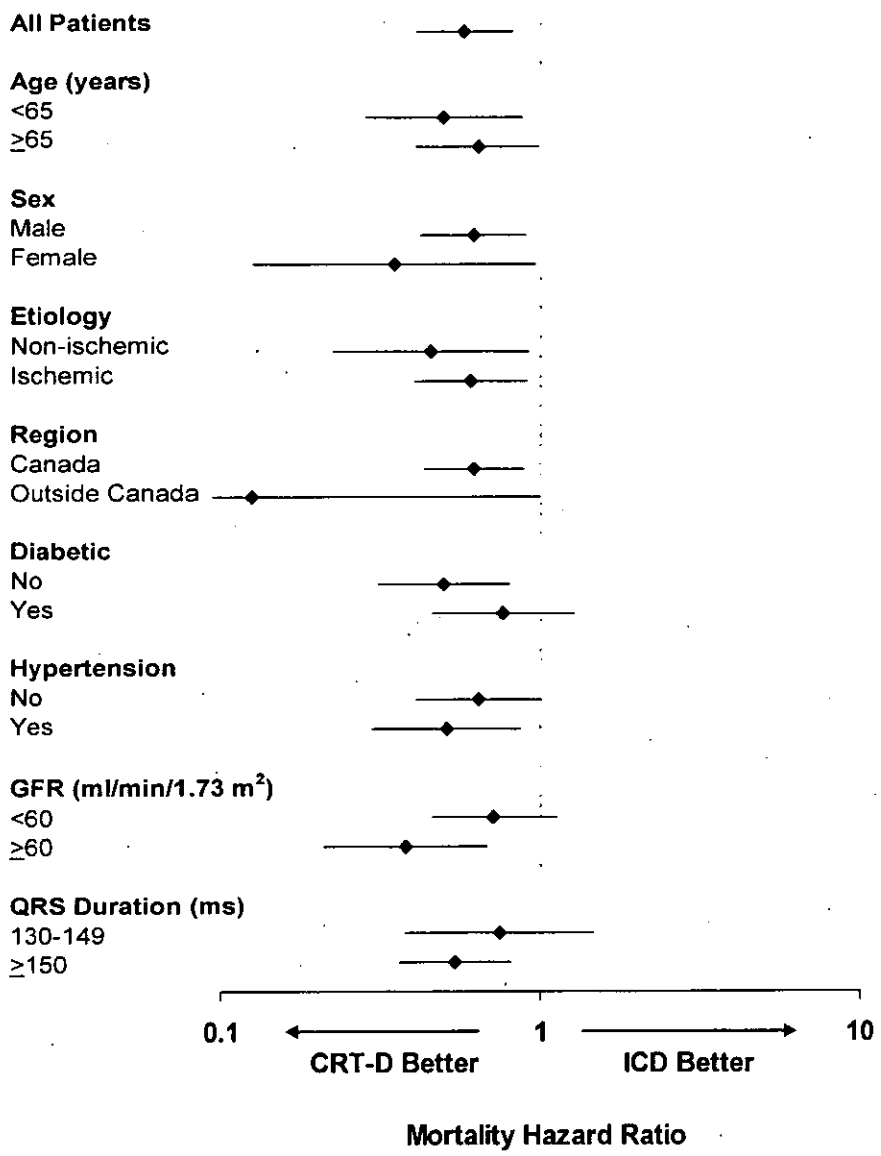


Figure 40: RAFT Mortality Subgroup Analysis - Expanded Indication Population (post-hoc analysis)



Gender Analysis

Additional subgroup analyses were performed by gender. In RAFT, both men and women demonstrated improvement with CRT-D over ICD. There was no significant difference in results for the primary endpoint - time to first heart failure hospitalization or death. There were some differences in baseline characteristics between males and females indicated by p-values < 0.05 as shown in Table 17.

Table 17: RAFT Baseline Demographics by Gender – NYHA Class II Cohort

Subject Characteristic	Female (n= 230)	Male (n= 1208)	P-value
Age (years)	64.8 ± 9.0	66.1 ± 9.4	0.047
LVEF (%)	23.0 ± 5.2	22.9 ± 5.1	0.79
QRS Duration (ms)	157.7 ± 23.6	157.8 ± 25.0	0.95
QRS Morphology Type RBBB LBBB IVCD Ventricular paced	 8% (18) 81% (187) 7% (16) 4% (9)	 10% (124) 71% (852) 12% (143) 7% (89)	0.008
Ischemic	42% (97)	70% (844)	<0.001
Diabetes	32% (74)	34% (406)	0.70
Hypertension	44% (102)	46% (557)	0.67
Beta blocker	87% (199)	91% (1096)	0.06
ACE-I/ARB	97% (222)	97% (1170)	0.84
Diuretic	85% (195)	82% (986)	0.30

Baseline characteristics by gender for the expanded indication population from RAFT are presented in Table 18.

Table 18: RAFT Baseline Demographics by Gender - Expanded Indication Population

Subject Characteristic	Female (n= 158)	Male (n= 692)	p-value
Age (years)	64.8 ± 8.7	64.9 ± 9.5	0.82
LVEF (%)	22.3 ± 5.1	22.5 ± 5.3	0.68
QRS Duration (ms)	163.5 ± 21.0	165.8 ± 22.1	0.22
QRS Morphology Type RBBB LBBB IVCD Ventricular paced	 0% (0) 100% (158) 0% (0) 0% (0)	 0% (0) 100% (692) 0% (0) 0% (0)	1.00
Ischemic	34% (53)	65% (447)	<0.001
Diabetes	26% (41)	32% (223)	0.13
Hypertension	42% (67)	46% (316)	0.48
Beta blocker	89% (140)	92% (638)	0.15

Subject Characteristic	Female (n= 158)	Male (n= 692)	p-value
ACE-I/ARB	97% (153)	97% (669)	1.00
Diuretic	85% (134)	80% (556)	0.22

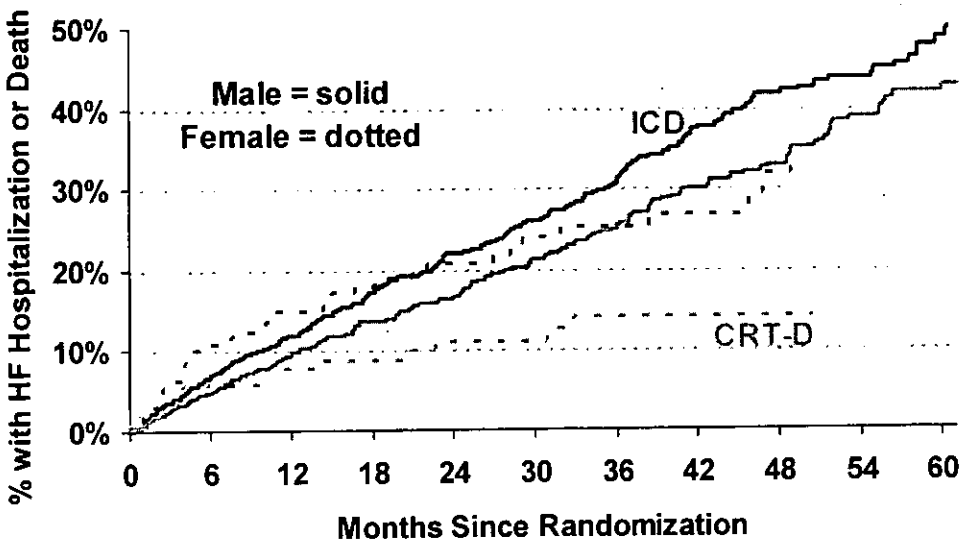
The proportion of female subjects enrolled in RAFT is lower than the gender-specific incidence or prevalence of heart failure in this patient population; however, similar to what has been observed in other trials of CRT.[2] In the RAFT NYHA Class II cohort, 84% of subjects were male and 16 % were female, and in the RAFT expanded indication population, 81% were male and 19% were female.

Analyses by gender for the RAFT NYHA Class II cohort and RAFT expanded indication population are presented below for the primary endpoint of time to first HF hospitalization or all-cause death, and for the secondary endpoint of mortality. P-values comparing male and female results are from the interaction term of Cox proportional hazards models. Terms fit in the models were randomization, gender, and their interaction.

Primary Endpoint

The primary endpoint results by gender for the NYHA Class II cohort are presented in Figure 41. There is no evidence of differences in CRT-D vs. ICD results between males and females (p=0.07). Both males and females showed improvement with CRT-D. Males had a hazard ratio of 0.77 (23% reduction in HF hospitalization or death), while females had a 0.43 hazard ratio.

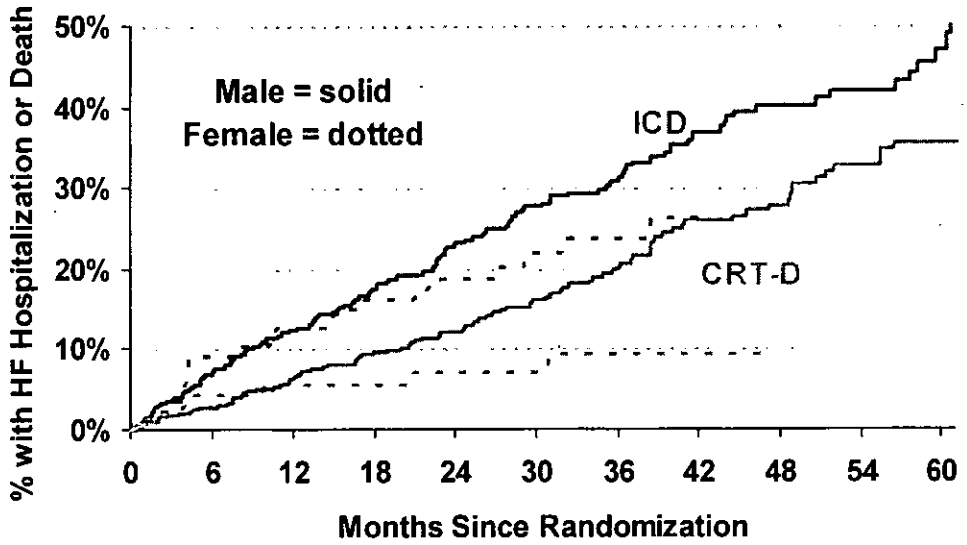
Figure 41: RAFT Time to First HF Hospitalization or All-cause Death by Gender – NYHA Class II Cohort



NR male	602	529	389	251	124	49
	606	547	414	269	159	65
NR female	128	109	76	49	23	8
	102	93	74	46	22	5

The primary endpoint results by gender for the expanded indication population can be seen in Figure 42. There is no evidence of differences in CRT-D vs. ICD results between males and females (p=0.16). Both males and females showed improvement with CRT-D. Males had a hazard ratio of 0.61 (39% reduction in HF hospitalization or death), while females had a 0.33 hazard ratio.

Figure 42: RAFT Time to First HF Hospitalization or All-cause Death by Gender - Expanded Indication Population

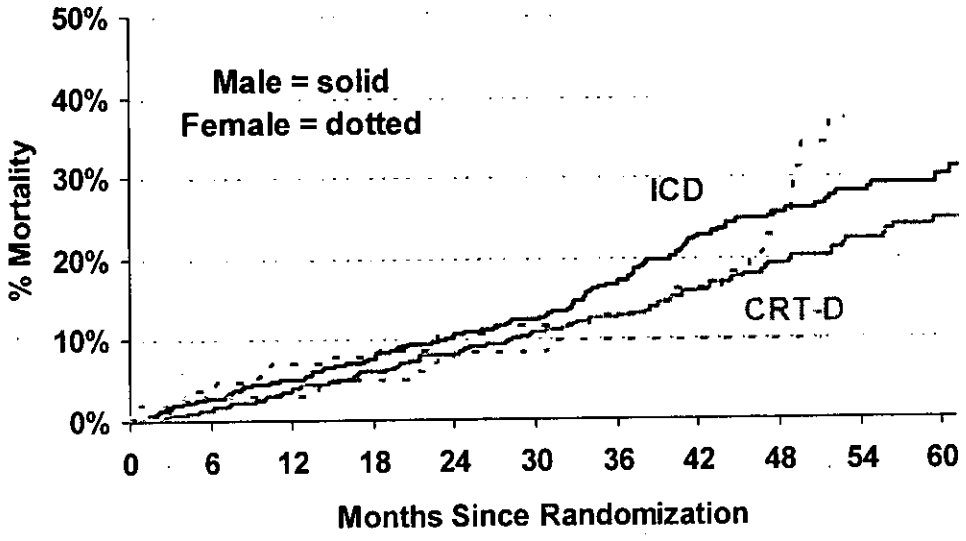


NR male	338	296	216	144	74	30
	354	332	256	174	106	45
NR female	128	109	76	49	23	8
	87	76	53	32	15	5

Secondary Endpoint

Mortality results by gender are presented in Figure 43. There is no evidence of differences in CRT-D vs. ICD results between males and females (p=0.29). Both males and females showed improvement with CRT-D. Males had a hazard ratio of 0.74 (26% reduction in mortality), while females had a 0.48 hazard ratio.

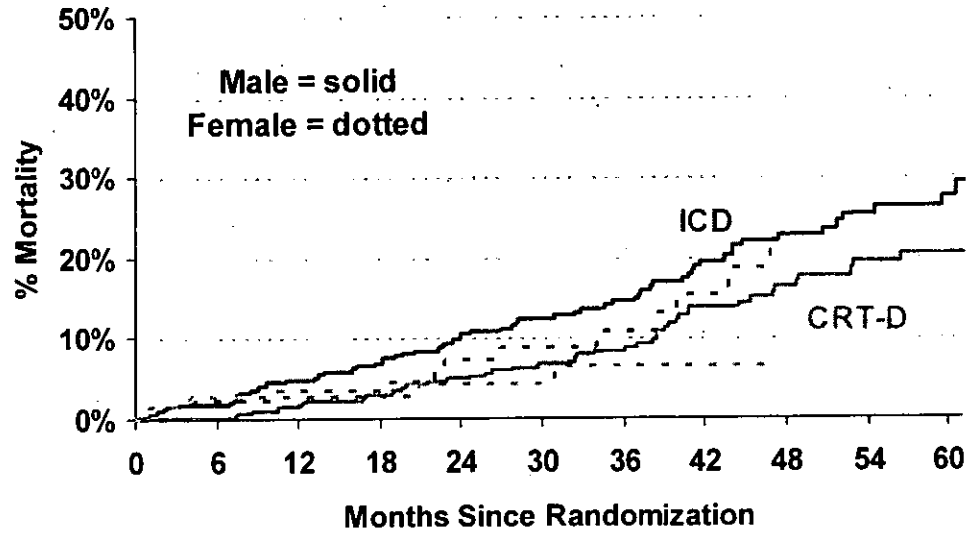
Figure 43: RAFT Mortality by Gender – NYHA Class II Cohort



NR male	602	568	446	307	162	73
	606	581	454	312	183	84
NR female	128	119	87	59	28	10
	102	98	76	49	24	5

Mortality results for the expanded indication population by gender can be seen in Figure 44. There is no evidence of differences in CRT-D vs. ICD results between males and females (p=0.33). Both males and females showed improvement with CRT-D. Males had a hazard ratio of 0.62 (38% reduction in mortality), while females had a 0.35 hazard ratio.

Figure 44: RAFT Mortality by Gender - Expanded Indication Population

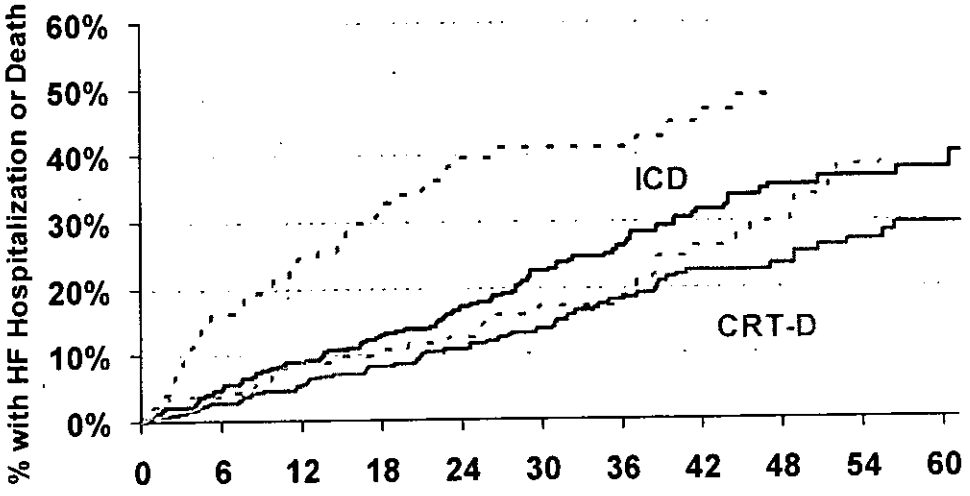


NR male	338	321	253	183	99	47
	354	349	276	198	118	53
NR female	87	84	62	41	18	5
	71	69	57	34	17	2

Previous Hospitalizations

A subgroup analysis was performed to compare primary endpoint results for the RAFT expanded indication population (Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II) between subjects who had been hospitalized overnight for heart failure within the 12 months prior to enrollment and those who had not as shown in Figure 45 below.

Figure 45: Time to First HF Hospitalization or All-cause Death by Previous HF Hospitalization - RAFT Expanded Indication Population



Number remaining					
No prev. hosp. 327	298	222	143	70	29
312	296	230	152	87	33
Prev. HF hosp. 98	74	47	33	19	6
113	103	82	55	35	14

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

A. Panel Meeting Recommendation

At an advisory meeting held on December 7, 2011, the Cardiovascular Devices Panel reviewed information presented by Medtronic and FDA, discussed the clinical data from the REVERSE and RAFT clinical studies, addressed the FDA questions, and voted. The following paragraphs summarize the discussion.

Regarding the REVERSE study, the Panel echoed many of FDA's concerns regarding the failed primary endpoint and the differences between the characteristics and study results in patients enrolled at sites in the U.S. versus sites outside the U.S. A significant portion of the discussion focused on the pooling of data from these populations. .Some members of the Panel indicated that the study did not demonstrate a mortality benefit.

Regarding the RAFT study, the Panel expressed concern that the RAFT study was not designed or conducted with the same amount of rigor as the REVERSE study, and the patients enrolled in RAFT were a higher risk population, which is supported by the higher background mortality rate. However, the RAFT study provides important supplemental data, which cannot be disregarded in the overall assessment of the sponsor's request.

Regarding both studies, the Panel expressed several concerns with the post-hoc selection of the proposed indicated population. However, the Panel indicated that the selection of the subgroup was logical, based on previous CRT studies and data presented in the literature. Panel members familiar with the therapy stated that CRT in general is beneficial. The Panel stated that the doses of heart failure medications used in the studies were consistent with those expected in a real-world setting, even if the doses were below those that might be expected in a randomized controlled trial. It was noted that patients did not experience subjective improvements in their status, as evaluated by multiple measures such as quality of life or 6-minute walk test distance. The Panel expressed concerns about the claims, especially use of a post-hoc selected subgroup from only the RAFT study to support those claims. Some members of the Panel questioned the use of a QRS duration of 120 milliseconds as a cut-off in the final indications and recommended that modified criteria be used to identify those patients most likely to benefit from the therapy.

Regarding safety, the Panel agreed that CRT systems are associated with a higher risk of complications related to the left ventricular lead. In addition, the longevity of a CRT-D device is less than the longevity of an ICD, requiring more frequent device replacement. Regarding the risks / benefit profile, the Panel did not identify any significant safety concerns in the studies, but some members of the Panel indicated that the benefits might not outweigh the risks in some patients less likely to benefit from CRT.

Regarding the post approval study, the Panel recommended that the study should include a pre-specified hypothesis with a control group for comparison purposes. The study should include a minimum number of female patients to ensure sufficient power for an analysis. In addition, the study should evaluate long-term mortality and heart failure events. Several options were discussed for identifying an appropriate control group and collecting the necessary data.

The Panel voted as follows:

- Question 1: The Panel voted 5-0 that there is reasonable assurance that the Medtronic CRT-Ds are safe for use in patients who meet the criteria specified in the proposed indication.

- Question 2: The Panel voted 3-2 that there is reasonable assurance that the Medtronic CRT-Ds are effective for use in patients who meet the criteria specified in the proposed indication.

- Question 3: The Panel voted 3-2 that the benefits of the Medtronic CRT-Ds do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

The materials for the meeting and summary for the panel meeting are available at the following link:

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm276551.htm

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, especially the concerns regarding the QRS duration of 120 milliseconds as a cut-off in indications for use statement. FDA and the company discussed the results, especially in those patients with QRS durations of 130-150 ms. While less compelling, these results are consistent with the overall results from the studies. As supplemental information, FDA also considered the general knowledge available within the clinical community including peer-reviewed journal articles. The company subsequently submitted an updated clinical report, with additional analyses focused on the results in patients with a QRS duration of greater than or equal to 130 ms. 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 consider a more restrictive cut-off for the QRS duration.

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.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

REVERSE Study

There was no pre-specified safety endpoint for the REVERSE study. However, adverse events and deaths were collected in the study and adjudicated by a blinded Adverse Event Advisory Committee (AEAC). A total of 608 adverse events were classified as procedure-, system-, or therapy-related at the time of the data cut-off. Among the 621 subjects that were successfully implanted with the CRT system, 77 had a total of 92 LV lead-related complications after their successful implant. The two (2) most common LV lead-related complications, accounting for 70% of these types of events, were LV lead dislodgement and diaphragmatic stimulation.

During the randomized period, 19 deaths occurred in the study: 7 in the CRT OFF group (3.7%), and 12 in the CRT ON group (2.9%). All deaths were adjudicated by the Adverse Event Advisory Committee (AEAC). The most common cause of death during the randomized period was progressive heart failure (4 of 19 deaths). At least 8 of the 19 (42.1%) deaths were from non-cardiac causes.

RAFT Study

Procedure- and system-related complications were collected at implant and each follow-up visit for the RAFT study. These complications were reviewed at DSMB meetings to ensure patient safety and adjudicated by a blinded Event Committee. No specific objective was pre-specified surrounding adverse events.

Of the 1798 randomized subjects, 1787 had an attempted device implant and accrued 5974 years of follow-up (ICD: n=899, 2923 years; CRT-D: n=888, 3051 years). During the study, 894 procedure- or system-related complications were reported in 583 subjects. In the ICD group, 24.9% of the subjects had at least one (1) procedure- or system-related complication during the study, and 40.4% of the subjects in the CRT-D group reported at least one (1). Much of the difference was due to expected battery depletion and subsequent device replacement in the CRT-D group. In the first 30 days post implant, 6.0% of the subjects in the ICD group had a procedure- or system-related complication, compared to 11.7% of the subjects in the CRT-D group. As all subjects in the RAFT study were indicated for an ICD, the incremental risk between the CRT-D group and the ICD group was the LV lead. There were 106 LV lead-related complications reported in the CRT-D group.

Total mortality was analyzed as a secondary objective for the study. During the study, 236 of 904 (26.1%) of ICD subjects died, and 186 of 894 (20.8%) of CRT-D subjects died. The hazard ratio was 0.75 in favor of CRT-D, which was statistically significant (p=0.003). At 5 years, the mortality rates were 34.6% in the ICD group and 28.6% in the CRT-D group.

B. Effectiveness Conclusions

REVERSE Study

The primary endpoint for the study was the Clinical Composite Response (CCR). A CCR was recorded at 12 months for all 610 randomized subjects. The Clinical Investigation Plan (CIP) pre-specified that a comparison would be made between the two (2) randomization groups based on the percentage of subjects worsened. In the full cohort, 21% of the CRT OFF group subjects worsened vs. 16% of the CRT ON group subjects. Although CRT ON resulted in a more favorable response, it did not achieve statistical significance at 12 months (p=0.10).

The primary endpoint was also analyzed for the expanded indication population: 18% of subjects in the CRT OFF group had a worsened CCR vs. 5% of the subjects in the CRT ON group.

RAFT Study

The primary effectiveness endpoint was met and was based on the composite endpoint of all-cause mortality and heart failure (HF) hospitalization measured at the time of the database lock (after all subjects had completed the 18-month follow-up

visit). Key effectiveness outcomes, including additional analyses supporting effectiveness, are presented below.

The primary endpoint for the study was time to first HF hospitalization or all-cause death. All hospitalizations greater than 24 hours were adjudicated by the blinded Adjudication Committee to be either heart failure related or not heart failure related. The primary outcome occurred in 364 of 904 subjects (40.3%) in the ICD group and 297 of 894 subjects (33.2%) in the CRT-D group. The hazard ratio was 0.75 in favor of CRT-D, which was statistically significant (p adjusted for interim analysis=0.014). At 5 years, the observed rates were 51.3% in the ICD group and 42.4% in the CRT-D group.

The primary endpoint was also analyzed for the expanded indication population. There was an observed 42% reduction in this endpoint with CRT-D. The estimated rate of HF hospitalization or all-cause death 4 years post-implant is 38.4% in the ICD group and 25.1% in the CRT-D group.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Medtronic CRT-D's when used in accordance with the indications for use.

The sponsor conducted two (2) separate large scale trials randomizing over 2400 patients in multiple countries in order to evaluate the benefits of CRT in an expanded population of patients. Despite a variety of limitations in the conduct and analysis of the studies, the overall results from these prospective studies are compelling, particularly in patients with a QRS duration of $\geq$ 150 ms. This is reflected in the comments of the two (2) Panel members who voted negatively on the effectiveness and risk/benefit questions. Those Panelists stated that had the cutoff been 150ms, not 120ms, they would have voted in favor.

On further review and consideration, FDA finds the results in patients with QRS durations of 130-150 ms, while less compelling, to be consistent with the overall results from the studies. FDA also considers the body of knowledge about CRT in this patient population that is available within the clinical community including peer-reviewed journal articles to be supportive of these results as supplemental confirmation of safety and effectiveness. Confirming this to be the case is the reason the Post Approval Study that Medtronic has agreed to conduct requires a minimum of 500 patients enrolled have QRS durations $\leq$ 150ms.

Based on the above, Medtronic has provided valid scientific data to demonstrate a reasonable assurance of safety and effectiveness for the expansion of indications for Medtronic CRT-D devices in heart failure patients who remain symptomatic despite optimal medical therapy and have left bundle branch block (LBBB) with a QRS duration $\geq$ 130 ms, left ventricular ejection fraction $\leq$ 30%, and NYHA Functional Class II.

XIII. CDRH DECISION

CDRH issued an approval order on April 4, 2012. The final conditions of approval cited in the approval order include an agreement to conduct two (2) post approval studies:

1. *REVERSE NCDR ICD Registry Study:* The study will consist of a newly enrolled prospective, observational study of US patients implanted with a Medtronic CRT-D device who meet the expanded indication identified American College of Cardiology (ACC) National Cardiovascular Data Registry (NCDR) Implantable Cardioverter Defibrillator (ICD) Registry.

   The primary study objective is to estimate the five-year survival probability for patients implanted with a Medtronic CRT-D device meeting the expanded indication criteria.

   Additional analyses will estimate the five-year survival probability by gender specific and QRS group.

   The study population will consist of adult patients treated with a Medtronic CRT-D device, meeting the expanded indication, who are identified through the ACC NCDR ICD Registry. Mortality through five years will be tracked for this cohort using the National Death Index. At least 1500 patients, with a minimum of 500 patients with a QRS < 150ms, will provide a two-sided confidence interval precision of 3% assuming a five-year survival probability of 75%.

   Within 30 days of your receipt of this letter, you must submit a separate PMA supplement that includes the complete protocol for your post-approval study. Your PMA supplements should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing.

2. *REVERSE Product Surveillance Registry:* The study will consist of a newly enrolled prospective, observational study of patients implanted with a Medtronic CRT-D device who meet the expanded indication with a QRS duration < 150ms enrolled into Medtronic's Product Surveillance Registry.

   The co-objectives are:

   - to estimate the 3-year survival probability of freedom from centrally adjudicated heart failure hospitalization or all-cause death for patients implanted with a Medtronic CRT-D device meeting the approved expanded indication criteria with a QRS duration < 150ms.

   - to estimate the 3-year survival probability of freedom from centrally adjudicated heart failure event or all cause death for patients implanted with a Medtronic CRT-D device meeting the approved expanded indication criteria with a QRS

duration < 150ms. Where a heart failure hospitalization event is defined as due to or associated with worsening heart failure with treatment either in-patient (hospitalization) or out-patient (emergency department, clinic, urgent care, etc.)

The study population will consist of adult patients treated with a Medtronic CRT-D device, meeting the expanded indication with a QRS duration < 150ms, enrolled into Medtronic's Product Surveillance Registry. Patients will be consented for follow-up through 5-years and actively followed approximately every 6 months from implant through a minimum of 3-years but potentially out to 5-years. Enrollment outside the US will be allowed but will be limited to no more than 40% of the total sample size. Assuming a three-year heart failure hospitalization or all-cause death proportion of 26.8%, a total of 500 patients will provide the ability to estimate the rate of patients with heart failure related hospitalization or all-cause death at 3 years with a 95% confidence interval within +/- 5%.

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

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