Boston Scientific

CLINICAL SUMMARY

# CONTAK CD

**CAUTION:** Federal law restricts this device to sale by or on the order of a physician trained or experienced in device implant and follow-up procedures.

Boston Scientific Corporation acquired Guidant Corporation in April 2006. During our transition period, you may see both the Boston Scientific and Guidant names on product and patient materials. As we work through the transition, we will continue to offer doctors and their patients technologically advanced and high quality medical devices and therapies.

## TABLE OF CONTENTS

# CLINICAL STUDY - CONTAK CD

## CLINICAL STUDY POPULATIONS

The CONTAK CD study results supported a CRT-D indication for those patients who had an indication for an ICD and and severe heart failure (NYHA III/IV) including left ventricular dysfunction (EF $\leq$ 35%) and QRS duration $\geq$ 120 ms and remained symptomatic despite stable, optimal heart failure drug therapy.

## SUMMARY

Guidant conducted the CONTAK CD Study to demonstrate the safety and effectiveness of the CONTAK CD system and to demonstrate a reasonable assurance of the safety and effectiveness of biventricular stimulation, or cardiac resynchronization therapy (CRT), using the Guidant Model 1822 VENTAK CHF AICD and Model 1823 CONTAK CD CRT-D along with the EASYTRAK (Models 4510/4511/4512/4513) coronary venous, steroid-eluting, single-electrode pace/sense lead.

The CONTAK CD Study failed to prospectively demonstrate effectiveness of the CRT portion of the device. The CONTAK CD Study met the Lead and System Effectiveness endpoints as well as the Lead and System Safety endpoints. Subgroup analysis revealed a population of patients that had Class III/IV heart failure at the time of randomization that appeared to have improvements on certain functional endpoints, including the Peak $VO_2$ and the Six-Minute Hall walk. A second study was performed (Focused Confirmatory Study) using this subgroup of patients to confirm the effectiveness of CRT.

## ADVERSE EVENTS

The VENTAK® CHF/CONTAK CD/EASYTRAK® Biventricular Pacing Study (hereafter referred to as the CONTAK CD Study) was a prospective, randomized, controlled, multicenter, double-blind study conducted at 47 sites in the United States and enrolled a total of 581 patients. Of these, 57 patients initially underwent a thoracotomy procedure to receive the Guidant Model 1822 VENTAK CHF AICD; 7 patients underwent a repeat procedure to receive an EASYTRAK lead. An additional 510 patients initially underwent an implant procedure to receive the Model 1823 CONTAK CD CRT-D along with the EASYTRAK (Models 4510/4511/4512/4513) coronary venous, single-electrode pace/sense lead for a total of 517 patients

who underwent an EASYTRAK lead implant procedure. In 69 patients the EASYTRAK lead implant attempt was unsuccessful.

Table 1 provides information on all adverse events reported from implant through the randomization period in patients attempted or implanted with the EASYTRAK lead. During this period, a total of 765 events were reported in 310 patients. Of these, 155 were classified as complications, and 610 were classified as observations.

**Table 1. Adverse Events Through the Randomization Period (Sheet 1 of 3)**
(765 Events in 517 patients implanted or attempted with the EASYTRAK lead, 2559 total device months)

| | # Of Events (# of pts)[a] | % Compli-cations (Patients) | Complica-tions per 100 Device Months (Events) | % Obser-vations (Patients) | Observations per 100 Device Months (Events) |
|---|---|---|---|---|---|
| **Total Adverse Events** | **765 (310)** | **23.4 (121)** | **6.0 (155)** | **51.8 (268)** | **23.5 (610)** |
| **PG-Related Events** | | | | | |
| Migration of device | 1 (1) | 0.0 (0) | 0.0 (0) | 0.2 (1) | 0.0 (1) |
| Pacemaker-mediated tachycardia (PMT) | 3 (3) | 0.0 (0) | 0.0 (0) | 0.6 (3) | 0.1 (3) |
| Telemetry difficulty | 1 (1) | 0.2 (1) | 0.0 (1) | 0.0 (0) | 0.0 (0) |
| **LV Lead-Related Events** | | | | | |
| Loss of capture | 43 (41) | 5.6 (29) | 1.1 (29) | 2.5 (13) | 0.5 (14) |
| Inappropriate shock due to oversensing | 1 (1) | 0.0 (0) | 0.0 (0) | 0.2 (1) | 0.0 (1) |
| Insulation breach observed | 1 (1) | 0.2 (1) | 0.0 (1) | 0.0 (0) | 0.0 (0) |
| Multiple counting[b] | 31 (22) | 1.0 (5) | 0.2 (5) | 3.9 (20) | 1.0 (26) |
| Phrenic nerve/diaphragm stimulation | 15 (15) | 0.4 (2) | 0.1 (2) | 2.5 (13) | 0.5 (13) |
| **RA Lead-Related Events** | | | | | |
| Loss of capture | 6 (6) | 1.0 (5) | 0.2 (5) | 0.2 (1) | 0.0 (1) |
| Oversensing | 3 (3) | 0.0 (0) | 0.0 (0) | 0.6 (3) | 0.1 (3) |
| Undersensing | 1 (1) | 0.2 (1) | 0.0 (1) | 0.0 (0) | 0.0 (0) |
| **RV Lead-Related Events** | | | | | |
| Loss of capture | 10 (9) | 0.6 (3) | 0.1 (3) | 1.2 (6) | 0.3 (7) |
| Elevated DFTs | 6 (6) | 0.4 (2) | 0.1 (2) | 0.8 (4) | 0.2 (4) |
| Inappropriate shock above rate cutoff | 49 (38) | 0.4 (2) | 0.1 (2) | 7.2 (37) | 1.8 (47) |
| Inappropriate shock due to oversensing | 5 (4) | 0.0 (0) | 0.0 (0) | 0.8 (4) | 0.2 (5) |
| Nonconversion of VF | 1 (1) | 0.2 (1) | 0.0 (1) | 0.0 (0) | 0.0 (0) |
| Oversensing | 2 (2) | 0.0 (0) | 0.0 (0) | 0.4 (2) | 0.1 (2) |
| Phantom shock | 2 (2) | 0.0 (0) | 0.0 (0) | 0.4 (2) | 0.1 (2) |
| Phrenic nerve/diaphragm stimulation | 5 (5) | 0.4 (2) | 0.1 (2) | 0.6 (3) | 0.1 (3) |
| **Subtotal Device-Related Events** | **186 (135)** | **9.5 (49)** | **2.1 (54)** | **19.0 (98)** | **5.1 (132)** |

**Table 1. Adverse Events Through the Randomization Period (Sheet 2 of 3)**
(765 Events in 517 patients implanted or attempted with the EASYTRAK lead, 2559 total device months)

| | # Of Events (# of pts)[a] | % Compli-cations (Patients) | Complica-tions per 100 Device Months (Events) | % Obser-vations (Patients) | Observations per 100 Device Months (Events) |
|---|---|---|---|---|---|
| **Procedure-Related Events** | | | | | |
| AV block | 7 (7) | 0.0 (0) | 0.0 (0) | 1.4 (7) | 0.3 (7) |
| Coronary sinus dissection | 5 (5) | 0.0 (0) | 0.0 (0) | 1.0 (5) | 0.2 (5) |
| Coronary venous perforation | 5 (5) | 0.2 (1) | 0.0 (1) | 0.8 (4) | 0.2 (4) |
| Hematoma | 11 (10) | 0.8 (4) | 0.2 (4) | 1.2 (6) | 0.3 (7) |
| Hypotension | 7 (7) | 0.0 (0) | 0.0 (0) | 1.4 (7) | 0.3 (7) |
| Infection, post-operative wound | 7 (7) | 0.6 (3) | 0.1 (3) | 0.8 (4) | 0.2 (4) |
| Pneumothorax | 7 (7) | 0.8 (4) | 0.2 (4) | 0.6 (3) | 0.1 (3) |
| Post surgical wound discomfort | 10 (9) | 0.2 (1) | 0.0 (1) | 1.5 (8) | 0.3 (9) |
| Renal failure | 5 (5) | 0.2 (1) | 0.0 (1) | 0.8 (4) | 0.2 (4) |
| Other[c] | 18 (18) | 1.2 (6) | 0.2 (6) | 2.3 (12) | 0.5 (12) |
| **Subtotal Procedure-Related Events** | **79 (71)** | **3.9 (20)** | **0.7 (17)** | **10.0 (51)** | **2.2 (56)** |
| **Cardiovascular-Related Events** | | | | | |
| AV Block | 3 (3) | 0.0 (0) | 0.0 (0) | 0.6 (3) | 0.1 (3) |
| Arrhythmia - SVT | 49 (42) | 0.2 (1) | 0.0 (1) | 7.9 (41) | 1.8 (48) |
| Arrhythmia - VT | 20 (17) | 1.0 (5) | 0.2 (5) | 2.7 (14) | 0.6 (15) |
| Arrhythmia - brady | 16 (14) | 0.2 (1) | 0.0 (1) | 2.5 (13) | 0.6 (15) |
| Cardiac arrest | 2 (2) | 0.4 (2) | 0.1 (2) | 0.0 (0) | 0.0 (0) |
| Chest pain | 30 (20) | 1.0 (5) | 0.2 (5) | 3.1 (16) | 1.0 (25) |
| Coagulopathy | 3 (3) | 0.2 (1) | 0.0 (1) | 0.4 (2) | 0.1 (2) |
| Congestive heart failure | 140 (91) | 3.5 (18) | 0.7 (18) | 16.1 (83) | 4.7 (122) |
| Distal thromboemboli | 3 (2) | 0.0 (0) | 0.0 (0) | 0.4 (2) | 0.1 (3) |
| Dizziness | 17 (17) | 0.0 (0) | 0.0 (0) | 3.3 (17) | 0.7 (17) |
| Dyspnea (shortness of breath) | 16 (13) | 0.0 (0) | 0.0 (0) | 2.5 (13) | 0.6 (16) |
| Fatigue | 10 (10) | 0.0 (0) | 0.0 (0) | 1.9 (10) | 0.4 (10) |
| Hypertension | 1 (1) | 0.0 (0) | 0.0 (0) | 0.2 (1) | 0.0 (1) |
| Hypotension | 11 (9) | 0.2 (1) | 0.0 (1) | 1.7 (9) | 0.4 (10) |
| Myocardial infarction | 2 (2) | 0.0 (0) | 0.0 (0) | 0.4 (2) | 0.1 (2) |
| Pacemaker syndrome | 1 (1) | 0.0 (0) | 0.0 (0) | 0.2 (1) | 0.0 (1) |
| Palpitations | 2 (2) | 0.0 (0) | 0.0 (0) | 0.4 (2) | 0.1 (2) |
| Pulmonary edema | 6 (6) | 0.4 (2) | 0.1 (2) | 0.8 (4) | 0.2 (4) |
| Shock | 4 (4) | 0.2 (1) | 0.0 (1) | 0.6 (3) | 0.1 (3) |
| Stroke syndrome or CVA | 4 (4) | 0.0 (0) | 0.0 (0) | 0.8 (4) | 0.2 (4) |

**Table 1. Adverse Events Through the Randomization Period (Sheet 3 of 3)**
(765 Events in 517 patients implanted or attempted with the EASYTRAK lead, 2559 total device months)

| | # Of Events (# of pts)[a] | % Compli-cations (Patients) | Complica-tions per 100 Device Months (Events) | % Obser-vations (Patients) | Observations per 100 Device Months (Events) |
|---|---|---|---|---|---|
| Syncope | 9 (9) | 0.0 (0) | 0.0 (0) | 1.7 (9) | 0.3 (9) |
| Thrombosis | 3 (3) | 0.0 (0) | 0.0 (0) | 0.6 (3) | 0.1 (3) |
| Vascular related | 6 (6) | 1.0 (5) | 0.2 (5) | 0.2 (1) | 0.0 (1) |
| **Subtotal Cardiovascular-Related Events** | **358 (200)** | **7.7 (40)** | **1.6 (42)** | **35.6 (184)** | **12.2 (316)** |
| **Total Noncardiovascular-Related Events** | **142 (92)** | **6.2 (32)** | **1.5 (39)** | **13.5 (70)** | **4.0 (103)** |

a. The total number of patients for a given event represents the unique number of patients who experienced that event. The total may not be equal to the sum of patients with complications or observations because some patients experienced more than one event that fell into both categories.
b. Sensing of the two ventricular intrinsic events when only one intrinsic event is present due to intraventricular conduction delay.
c. Other procedure-related events occurred in three patients or fewer: Guide wire fracture (1), Hemorrhage (3), Finishing wire left in lead (1), Nonconversion of VF (1), Perforation, arterial (1), Perforation, cardiac (1), Perforation, venous (2), Pericardial effusion (3), Pericarditis (1), Physiological reaction (1).

## Deaths

A total of 109 deaths occurred during the study. These deaths occurred during the study periods as shown in Table 2 along with the cause of death as adjudicated by an independent events committee.

**Table 2. Deaths that Occurred During the Study**
(All patients enrolled, N = 581)

| Study Period | # of pt deaths | Cause of Death | | | | |
|---|---|---|---|---|---|---|
| | | Cardiac: Pump Failure | Cardiac: Arrhythmic | Cardiac: Other | Non-cardiac | Unknown |
| After unsuccessful implant procedure | 2 | 1 | 1 | 0 | 0 | 0 |
| Peri-operative (≤ 30 days) | 10 | 5 | 2 | 0 | 2 | 1 |
| Randomized therapy phase[a]: No CRT | 16 | 9 | 0 | 1 | 3 | 3 |
| Randomized therapy phase[a]: CRT | 11 | 4 | 1 | 2 | 2 | 2 |
| Post-randomized therapy phase[b] | 70 | 28 | 5 | 1 | 16 | 20 |
| **Total** | **109** | **47** | **9** | **4** | **23** | **26** |

a. Day 31 to 120 for Phase I patients, day 31 to 210 for Phase II patients.
b. Day 121 and beyond for Phase I patients, day 211 and beyond for Phase II patients.

# STUDY DESIGN

The CONTAK CD Study was a prospective, randomized, controlled, multicenter, double-blind study conducted at 47 sites in the United States and enrolled a total of 581 patients. All patients enrolled were intended to be implanted with a device capable of delivering both CRT and treating ventricular tachyarrhythmias. Patients were randomized to CRT Off (VVI lower rate 40) or CRT On (VDD). The study began as a crossover design (called "Phase I") and enrolled 248 patients with a primary endpoint of functional status with three months of follow-up. The study was later modified to a parallel design (called "Phase II") and enrolled 333 patients with a longer, six-month follow-up. The data from the first three months of the crossover phase were pooled with data obtained from the six-month parallel phase. The visit schedule and testing requirements remained the same. Additionally, while the study originally used the VENTAK CHF AICD in conjunction with epicardial leads placed via thoracotomy, the CONTAK CD CRT-D and EASYTRAK lead (placed transvenously) were added to the protocol later in the study.

## Inclusion/Exclusion Criteria

Patients enrolled in the study were required to meet the following inclusion criteria:

- Meet the general indication for ICD implant
- Symptomatic heart failure despite optimal drug therapy (ACE inhibitors with diuretic and/or digoxin, as determined to be indicated and tolerated by the patient's physician-investigator)
- Left ventricular ejection fraction ≤ 35%
- QRS duration ≥ 120 ms
- Age ≥ 18 years
- Normal sinus node function

Patients were excluded from the investigation if they met any of the following criteria:

- Meet the general indications for permanent antibradycardia pacing, including pacemaker dependence
- Have chronic, medically refractory atrial tachyarrhythmias
- Require concomitant cardiac surgery
- Are unable to undergo device implant, including general anesthesia if required
- Are unable to comply with the protocol and follow-up requirements, including exercise testing
- Have a life expectancy of less than six months due to other medical conditions

- Have amyloid disease (amyloidosis)
- Have hypertrophic obstructive cardiomyopathy
- Require in-hospital continuous intravenous inotropes
- Have pre-existing cardioversion/defibrillation leads other than those specified in this investigational plan (unless the investigator intends to replace them with permitted cardioversion/defibrillation leads)
- Women who are pregnant or not using medically accepted birth control
- Have a mechanical tricuspid prosthesis
- Involved in other cardiovascular clinical investigations of active therapy or treatment

### Follow-up Schedule

| | |
|---|---|
| Pre-implant visit | Initial assessment of patient eligibility; taking of patient history. |
| Implant | Implant of investigational devices and acute device testing. Randomization status (CRT or No CRT) was assigned for implementation after a 30-day Recovery Period. |
| Recovery Period | Minimum 30-day period over which the patient recovered from the implant procedure and had his/her heart failure medications adjusted, but with no CRT, regardless of the randomization assignment. |
| Post-Recovery Visit | First visit after the Recovery Period in which patients underwent Special Testing[a] to establish their baseline condition, after which the randomization assignment was implemented (CRT or No CRT). |
| Three- and six-month visit | Evaluation of randomized therapy with Special Testing[a] and device function at three- and six-months after the Post-Recovery Visit. |
| Quarterly Visits | After the six-month visit, patients were seen for routine evaluation of device function and patient condition. |

a. Special Testing included a Symptom-Limited Treadmill Test with measurement of oxygen uptake (Peak $VO_2$), a Six-Minute Walk, Echocardiography, Holter monitoring, blood chemistry testing, and a Quality of Life (QOL) questionnaire.

## STUDY RESULTS

### Demographic Data

The CONTAK CD Study included patients with symptomatic heart failure despite optimal drug therapy as defined in the inclusion criteria. The population included patients who were NYHA Class II, III, or IV at the time of implant.

Based upon the clinical results from the covariate analyses in this study and the internal consistency of these clinical findings with those from other completed CRT studies, the patient subgroup with NYHA Class III/IV heart failure in this study was examined further.

- ***All Patients:*** All patients (NYHA Class II/III/IV at the time of implant) implanted with an investigational system (N = 501). Ten patients died and one withdrew before the post-recovery visit. Therefore, therapy effectiveness analyses used N = 490.

- **NYHA Class III/IV (Advanced Heart Failure):** This subgroup was defined as those patients with moderate to severe heart failure at the time of the Post-Recovery Visit (N = 227). A percentage of patients either had an improvement or worsening of their NYHA Class during the post-implant recovery period. The patients in the Advanced Heart Failure subgroup were only those who remained in NYHA Class III/IV at the end of the post-recovery period. This subgroup was determined from interaction analysis of preselected covariates with the functional status endpoints.

## Endpoints

The CONTAK CD Study had three investigational elements consisting of:

***CRT Effectiveness:***

**Primary:** Composite endpoint consisting of all-cause mortality, hospitalization for heart failure, and ventricular tachyarrhythmia requiring device intervention.

**Secondary:** Peak $VO_2$ derived from a symptom-limited exercise test and Quality of Life as measured by the Minnesota Living with Heart Failure Questionnaire©.

**Additional:** Six-Minute Walk, NYHA Class, Echocardiographic Analysis, Change in Norepinephrine, and Change in Heart Rate.

***Lead and System Effectiveness:***

**Lead:** Left ventricular pacing thresholds, biventricular sensing, biventricular lead impedance, and lead placement success rate.

**System:** VF detection time and biventricular antitachycardia pacing (ATP) effectiveness.

***Lead and System Safety:***

**Lead:** Incidence of lead-related adverse events.

**System:** Incidence of severe, device-related adverse events and operative mortality.

## Patient Accountability

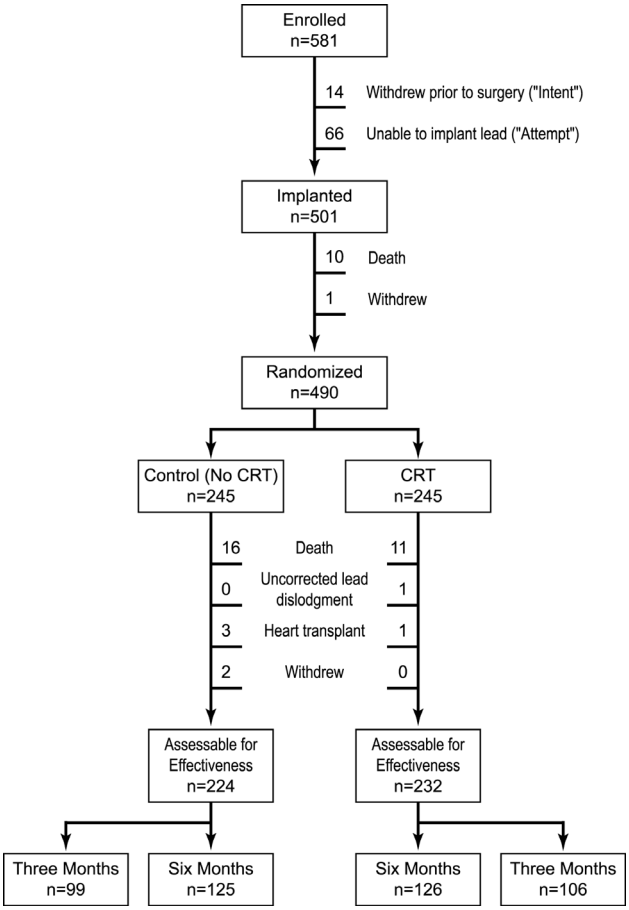


**Figure 1. Enrollment and follow-up of randomized patients.**

# Baseline Characteristics

**Table 3. Pre-Implant Assessment**
**(**All Patients Implanted, N=501)

| Characteristic | | All Patients | | | NYHA Class III/IV | | |
|---|---|---|---|---|---|---|---|
| | | CRT (N = 248) | No CRT (N = 253) | P-val[a] | CRT (N = 117) | No CRT (N = 110) | P-val[a] |
| Age at Implant (years) | N | 248 | 253 | | 117 | 110 | |
| | Mean +/- SD | 66.0 +/- 10.5 | 66.3 +/- 10.5 | 0.73 | 66.1 +/- 10.5 | 65.8 +/- 10.5 | 0.80 |
| | Range | 26.1 - 82.6 | 29.5 - 86.3 | | 26.1 - 82.5 | 38.3 - 85.3 | |
| Gender [N (%)] | Male | 210 (84.7) | 211 (83.4) | 0.70 | 90 (76.9) | 86 (78.2) | 0.82 |
| | Female | 38 (15.3) | 42 (16.6) | | 27 (23.1) | 24 (21.8) | |
| NYHA Class [N (%)] | II | 80 (32.3) | 83 (32.8) | 0.66 | 20 (17.1) | 11 (10.0) | 0.08 |
| | III | 148 (59.7) | 144 (56.9) | | 85 (72.6) | 78 (70.9) | |
| | IV | 20 (8.1) | 26 (10.3) | | 12 (10.3) | 21 (19.1) | |
| Concomitant Medications [N (%)] | ACE or ARB | 212 (85.5) | 224 (88.5) | 0.31 | 95 (81.2) | 98 (89.1) | 0.10 |
| | Beta Blocker | 119 (48.0) | 117 (46.2) | 0.70 | 53 (45.3) | 44 (40.0) | 0.42 |
| | Digoxin | 172 (69.4) | 171 (67.6) | 0.67 | 84 (71.8) | 75 (68.2) | 0.55 |
| | Diuretic | 217 (87.5) | 210 (83.0) | 0.16 | 108 (92.3) | 95 (86.4) | 0.15 |
| Qualifying LVEF (%) | N | 248 | 253 | | 117 | 110 | |
| | Mean +/- SD | 21.4 +/- 6.6 | 21.5 +/- 6.7 | 0.74 | 20.6 +/- 6.4 | 21.1 +/- 6.2 | 0.61 |
| | Range | 5.0 - 35.0 | 10.0 - 35.0 | | 8.0 - 35.0 | 10.0 - 35.0 | |
| PR Interval[b] (ms) | N | 224 | 222 | | 107 | 91 | |
| | Mean +/- SD | 205 +/- 42 | 202 +/- 49 | 0.44 | 204 +/- 41 | 200 +/- 54 | 0.60 |
| | Range | 88 - 336 | 104 - 400 | | 136 - 336 | 110 - 400 | |
| Qualifying QRS Duration[b] (ms) | N | 226 | 224 | | 109 | 93 | |
| | Mean +/- SD | 160 +/- 27 | 156 +/- 26 | 0.06 | 164 +/- 27 | 152 +/- 24 | < 0.01 |
| | Range | 120 - 240 | 120 - 264 | | 120 - 240 | 120 - 222 | |
| Resting Heart Rate (bpm) | N | 248 | 253 | | 117 | 110 | |
| | Mean +/- SD | 73 +/- 12 | 75 +/- 14 | 0.37 | 75 +/- 13 | 74 +/- 15 | 0.61 |
| | Range | 43 - 108 | 48 - 120 | | 43 - 108 | 50 - 120 | |
| Systolic Blood Pressure (mmHg) | N | 247 | 253 | | 116 | 110 | |
| | Mean +/- SD | 118 +/- 21 | 118 +/- 21 | 0.95 | 116 +/- 20 | 117 +/- 23 | 0.72 |
| | Range | 79 - 197 | 70 - 190 | | 79 - 191 | 74 - 190 | |
| Diastolic Blood Pressure (mmHg) | N | 247 | 253 | | 116 | 110 | |
| | Mean +/- SD | 67 +/- 12 | 69 +/- 12 | 0.27 | 68 +/- 12 | 67 +/- 14 | 0.85 |
| | Range | 31 - 100 | 40 - 109 | | 31 - 100 | 40 - 109 | |

a. P-values for comparing means were calculated with Student's t-test; p-values for comparing proportions were calculated with Pearson's chi-squared test.
b. PR interval and QRS duration were not obtained for thoracotomy patients.

**Table 4. Pre-Implant History**
(All Patients Implanted, N = 501)

| Characteristic | | All Patients | | | NYHA Class III/IV | | |
|---|---|---|---|---|---|---|---|
| | | CRT (N = 248) | No CRT (N = 253) | P-val[a] | CRT (N = 117) | No CRT (N = 110) | P-val[a] |
| Primary Tachyarrhythmia [N (%)] | Monomorphic VT (MVT) | 148 (59.7) | 136 (53.8) | 0.44 | 72 (61.5) | 48 (43.6) | 0.03 |
| | Polymorphic VT (PVT) | 16 (6.5) | 20 (7.9) | | 7 (6.0) | 7 (6.4) | |
| | Nonsustained VT | 58 (23.4) | 63 (24.9) | | 30 (25.6) | 35 (31.8) | |
| | Ventricular Fibrillation (VF) | 26 (10.5) | 32 (12.6) | | 8 (6.8) | 18 (16.4) | |
| | Other | 0 (0.0) | 2 (0.8) | | 0 (0.0) | 2 (1.8) | |
| Other Arrhythmias [N (%)] | Paroxysmal Atrial Fibrillation | 43 (17.3) | 62 (24.5) | 0.05 | 21 (17.9) | 29 (26.4) | 0.13 |
| | Atrial Flutter | 10 (4.0) | 13 (5.1) | 0.55 | 3 (2.6) | 7 (6.4) | 0.16 |
| Arrhythmia/ Conduction Disorder [N (%)] | LBBB | 133 (53.6) | 138 (54.5) | 0.83 | 59 (50.4) | 59 (53.6) | 0.55 |
| | RBBB | 35 (14.1) | 31 (12.3) | | 21 (17.9) | 14 (12.7) | |
| | Non-Specific | 80 (32.3) | 84 (33.2) | | 37 (31.6) | 37 (33.6) | |
| Etiology [N (%)] | Ischemic | 167 (67.3) | 178 (70.4) | 0.47 | 76 (65.0) | 78 (70.9) | 0.34 |
| | Non-Ischemic | 81 (32.7) | 75 (29.6) | | 41 (35.0) | 32 (29.1) | |

a. P-values were calculated with Pearson's chi-squared test.

## CRT Effectiveness

### *Heart Failure Progression (Composite Index)*

The Composite Index (primary endpoint) was a combination of three events: all-cause mortality, hospitalization for heart failure, and VT/VF event requiring therapy (Table 5). A committee consisting of three heart failure specialists and an electrophysiologist reviewed and adjudicated all patient deaths and all hospitalizations, defined as an admission greater than 23 hours. Outpatient care, emergency room care, and clinic visits less than 23 hours were collected but not considered to be hospitalizations for the purposes of analysis.

**Table 5. Composite Index (Sheet 1 of 2)**
**(**All patients implanted and active 31 days post-implant)

| Group | Heart Failure Mortality or Morbidity Event | CRT | | No CRT | | Relative Reduction with CRT |
|---|---|---|---|---|---|---|
| | | N | % | N | % | |
| All Patients (N = 490) | Death from any cause | 11 | 4.5 | 16 | 6.5 | 15% p = 0.35 |
| | HF hospitalization | 32 | 13.1 | 39 | 15.9 | |
| | VT/VF | 36 | 14.7 | 39 | 15.9 | |

**Table 5. Composite Index (Sheet 2 of 2)**
**(**All patients implanted and active 31 days post-implant)

| Group | Heart Failure Mortality or Morbidity Event | CRT | | No CRT | | Relative Reduction with CRT |
|---|---|---|---|---|---|---|
| | | N | % | N | % | |
| NYHA Class III/IV (N = 227) | Death from any cause | 11 | 9.4 | 11 | 10.0 | 22% p = 0.23 |
| | HF hospitalization | 23 | 19.7 | 27 | 24.5 | |
| | VT/VF | 21 | 17.9 | 22 | 20.0 | |

Twenty-seven patients died during the therapy phase. Mortality stratified by treatment group and cause, as adjudicated by the Events Committee, is shown in Table 6. The Kaplan-Meier curve, showing total survival by treatment group, is shown in Figure 2.

**Table 6. Mortality Stratified by Treatment Group and Cause**
(All patients implanted and active at 31 days post-implant, N = 490)

| Deaths | Patients with CRT (N = 245) | Patients with No CRT (N = 245) |
|---|---|---|
| Cardiac, pump failure | 4 (1.6%) | 9 (3.7%) |
| Cardiac, arrhythmic | 1 (0.4%) | 0 (0.0%) |
| Cardiac, other | 2 (0.8%) | 1 (0.4%) |
| Noncardiac | 2 (0.8%) | 3 (1.2%) |
| Unknown | 2 (0.8%) | 3 (1.2%) |
| **Total** | **11 (4.5%)** | **16 (6.5%)** |

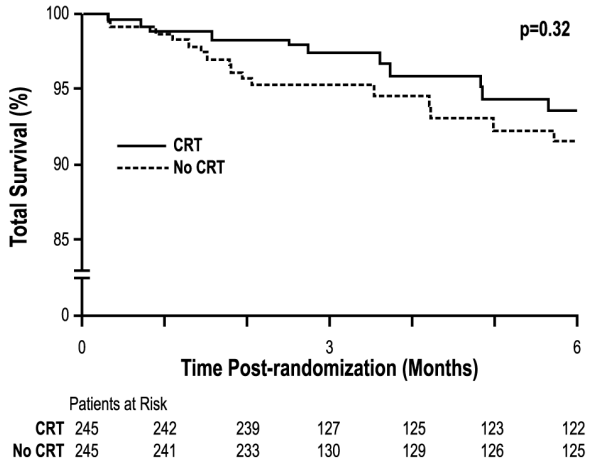


**Figure 2. Kaplan-Meier curve.**

Table 7 presents the reasons for hospitalization within the treatment period as determined by the Events Committee.

**Table 7. Patients Hospitalized during Treatment Period[a]**
(All patients implanted and active at 31 days post-implant, N = 490)

| Reason for Hospitalization | All Patients | | | NYHA Class III/IV | | |
|---|---|---|---|---|---|---|
| | CRT (N = 245) | No CRT (N = 245) | Total (N = 490) | CRT (N = 117) | No CRT (N = 110) | Total (N = 227) |
| Heart failure | 32 | 39 | 71 | 23 | 27 | 50 |
| Cardiac, other | 20 | 25 | 45 | 14 | 14 | 28 |
| Noncardiac | 26 | 19 | 45 | 14 | 14 | 28 |
| **Total Hospitalizations** | **66** | **70** | **136** | **40** | **46** | **86** |

a. Represents number of patients with each category of hospitalization. Patients may have multiple hospitalizations that fall into different categories.

## Peak $VO_2$

The Peak $VO_2$ was determined from a standardized protocol for exercise testing as a means of measuring a patient's capacity for performing physical activity. Figure 3 and the accompanying table provide the change in Peak $VO_2$.

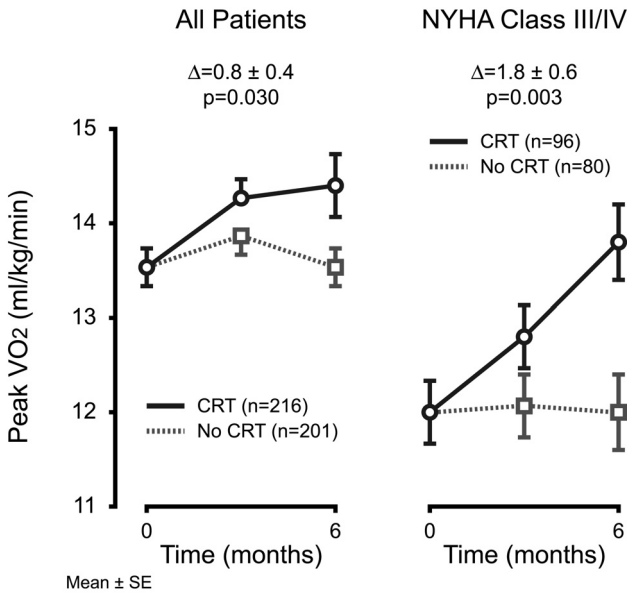


**Figure 3. Change in Peak $VO_2$**

| Peak $VO_2$ (ml/kg/min) | All Patients | | | NYHA Class III/IV | | |
|---|---|---|---|---|---|---|
| | CRT (N = 216) | No CRT (N = 201) | P-val[a] | CRT (N = 96) | No CRT (N = 80) | P-val[a] |
| Post-recovery Visit | 13.5 +/- 0.2 | 13.5 +/- 0.2 | - | 12.0 +/- 0.3 | 12.0 +/- 0.3 | - |
| 3 Months | 14.3 +/- 0.2 | 13.9 +/- 0.2 | 0.206 | 12.8 +/- 0.4 | 12.1 +/- 0.4 | 0.084 |
| 6 Months | 14.4 +/- 0.3 | 13.6 +/- 0.3 | 0.030 | 13.8 +/- 0.5 | 12.0 +/- 0.5 | 0.003 |

a. P-values reflect the between-group differences with respect to baseline.

## Six-Minute Walk

The Six-Minute Walk test is a measure of a patient's ability to sustain exercise during an activity similar to that which a patient may typically perform on a daily basis. For this test, patients are instructed to walk as far as possible in 6 minutes in a level

corridor. Figure 4 and the accompanying table provide the change in Six-Minute Walk.

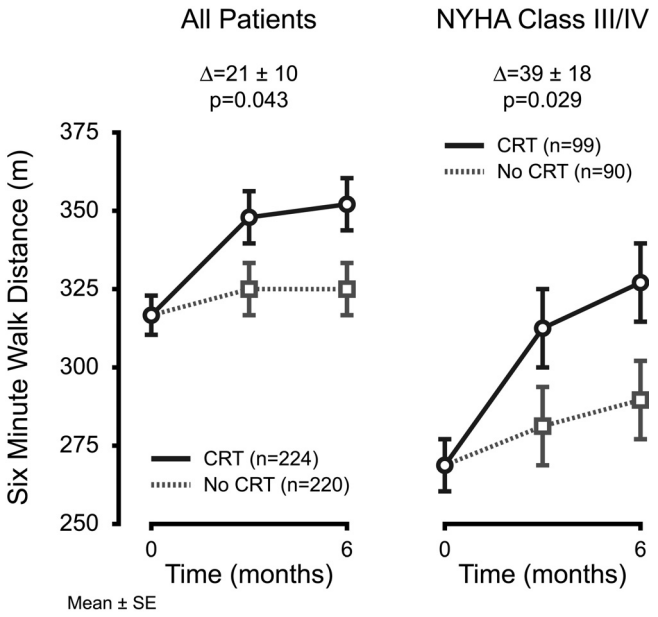


**Figure 4. Change in Six-Minute Walk**

| Six Minute Walk Distance (meters) | All Patients | | | NYHA Class III/IV | | |
|---|---|---|---|---|---|---|
| | CRT (N = 224) | No CRT (N = 220) | P-val[a] | CRT (N = 99) | No CRT (N = 90) | P-val[a] |
| Post-recovery Visit | 317 +/- 5 | 317 +/- 5 | - | 268 +/- 9 | 268 +/- 9 | - |
| 3 Months | 348 +/- 7 | 331 +/- 8 | 0.058 | 312 +/- 12 | 280 +/- 12 | 0.028 |
| 6 Months | 353 +/- 8 | 332 +/- 8 | 0.043 | 327 +/- 14 | 288 +/- 15 | 0.029 |

a. P-values reflect the between-group differences with respect to baseline.

## Quality of Life

Quality of Life (QOL) was assessed using the 21-question Minnesota Living with Heart Failure questionnaire. Each question is answered by the patient, ranking each

item on a scale ranging from 0 to 5. A lower total score indicates an improved quality of life. Figure 5 and the accompanying table provide the change in Quality of Life.

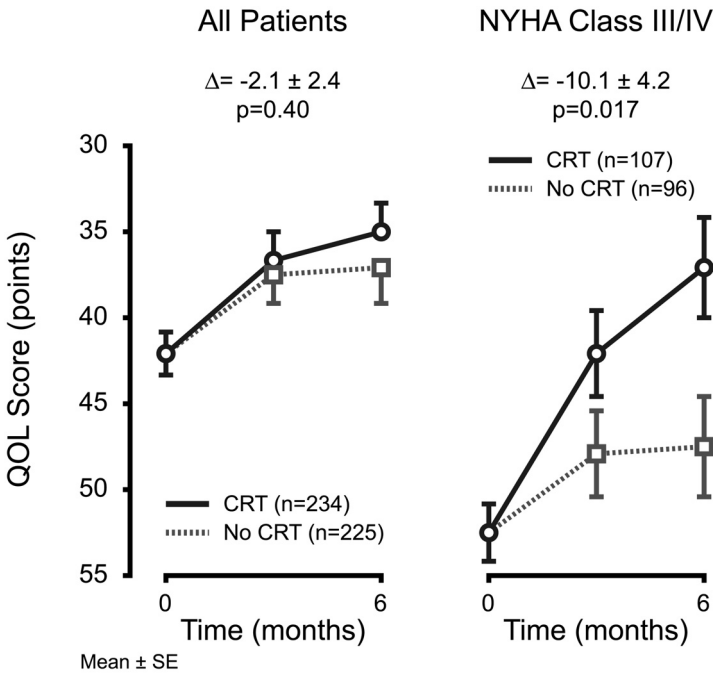


**Figure 5. Change in Quality of Life**

| QOL (points) | All Patients | | | NYHA Class III/IV | | |
|---|---|---|---|---|---|---|
| | CRT (N = 234) | No CRT (N = 225) | P-val[a] | CRT (N = 107) | No CRT (N = 96) | P-val[a] |
| Post-recovery Visit | 41.8 +/- 1.1 | 41.8 +/- 1.1 | - | 52.7 +/- 1.5 | 52.7 +/- 1.5 | - |
| 3 Months | 36.6 +/- 1.5 | 37.3 +/- 1.6 | 0.711 | 41.9 +/- 2.4 | 47.5 +/- 2.6 | 0.078 |
| 6 Months | 34.8 +/- 1.8 | 36.9 +/- 1.8 | 0.395 | 37.2 +/- 3.1 | 47.3 +/- 3.2 | 0.017 |

a. P-values reflect the between-group differences with respect to baseline.

## NYHA Class

The determination of New York Heart Association (NYHA) Class is based on mutual assessment by the patient and the patient's physician of the patient's heart failure symptoms both at rest and while performing ordinary physical activity. NYHA Class

was determined at each follow-up visit by a physician who was blinded to the patient's randomized therapy. Figure 6 and the accompanying table provide the change in NYHA Class results.

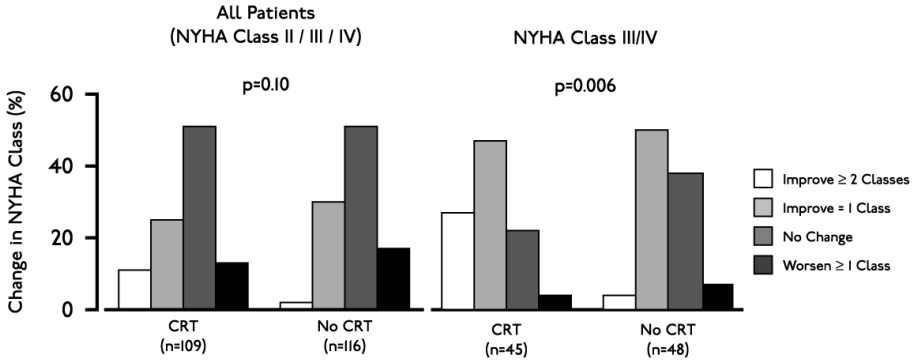


**Figure 6. Change in NYHA Class**

| Change in NYHA Class | All Patients | | | | | NYHA Class III/IV | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CRT (N = 109) | | No CRT (N = 116) | | P-val[a] | CRT (N = 45) | | No CRT (N = 48) | | P-val[a] |
| | N | % | N | % | | N | % | N | % | |
| Improve 2 or More Classes | 12 | 11.0 | 2 | 1.7 | 0.10 | 12 | 26.7 | 2 | 4.2 | 0.006 |
| Improve 1 Class | 27 | 24.8 | 35 | 30.2 | | 21 | 46.7 | 24 | 50.0 | |
| No Change | 56 | 51.4 | 59 | 50.9 | | 10 | 22.2 | 18 | 37.5 | |
| Worsen 1 Class | 13 | 11.9 | 19 | 16.4 | | 2 | 4.4 | 4 | 8.3 | |
| Worsen 2 or More Classes | 1 | 0.9 | 1 | 0.9 | | 0 | 0.0 | 0 | 0.0 | |

a. P-value was calculated from Mantel-Haenszel test and reflects the between-group differences with respect to baseline.

## Echocardiography

Several echocardiography (echo) variables were identified to assist in measuring the possible hemodynamic impact of CRT as shown in Table 8. The limitation of this data is that patients are measured while at rest, and therefore, the data may not reflect any hemodynamic benefit that may be observed when patients are exercising and performing their daily activities.

**Table 8. Echocardiography Results**

| Parameter | Timepoint | CRT | | No CRT | | Between Groups | |
|---|---|---|---|---|---|---|---|
| | | N | Mean +/- SE | N | Mean +/- SE | Mean +/- SE | P-val |
| **All Patients** | | | | | | | |
| LVIDd (mm) | Post-recovery Visit | 228 | 70.4 +/- 0.5 | 219 | 70.4 +/- 0.5 | 0 | - |
| | Change at 6 Months | 228 | -3.4 +/- 0.6 | 219 | -0.3 +/- 0.6 | -3.1 +/- 0.9 | < 0.001 |
| LVIDs (mm) | Post-recovery Visit | 228 | 58.3 +/- 0.5 | 219 | 58.3 +/- 0.5 | 0 | - |
| | Change at 6 Months | 228 | -4.0 +/- 0.7 | 219 | -0.7 +/- 0.7 | -3.3 +/- 0.9 | < 0.001 |
| LVEF (%) | Post-recovery Visit | 222 | 27.8 +/- 0.3 | 216 | 27.8 +/- 0.3 | 0 | - |
| | Change at 6 Month | 222 | 5.1 +/- 0.7 | 216 | 2.8 +/- 0.7 | 2.4 +/- 1.0 | 0.020 |
| **NYHA Class III/IV** | | | | | | | |
| LVIDd (mm) | Post-recovery Visit | 104 | 71.2 +/- 0.7 | 92 | 71.2 +/- 0.7 | 0 | - |
| | Change at 6 Months | 104 | -4.9 +/- 1.0 | 92 | -0.2 +/- 1.1 | -4.7 +/- 1.5 | 0.001 |
| LVIDs (mm) | Post-recovery Visit | 104 | 59.2 +/- 0.7 | 92 | 59.2 +/- 0.7 | 0 | - |
| | Change at 6 Months | 104 | -5.4 +/- 1.1 | 92 | -0.6 +/- 1.1 | -4.8 +/- 1.5 | 0.002 |
| LVEF (%) | Post-recovery Visit | 99 | 26.9 +/- 0.5 | 91 | 26.9 +/- 0.5 | 0 | - |
| | Change at 6 Months | 99 | 6.0 +/- 1.1 | 91 | 2.3 +/- 1.2 | 3.7 +/- 1.7 | 0.029 |

## Measures of Sympathetic Tone

Mean Norepinephrine levels (Table 9) and Mean Heart Rate (Table 10) were examined as markers of how CRT may influence the excessive sympathetic drive associated with chronic heart failure.

**Table 9. Mean Norepinephrine Results**

| Norepinephrine (pg/mL) | All Patients | | | NYHA Class III/IV | | |
|---|---|---|---|---|---|---|
| | CRT (N = 228) | No CRT (N = 217) | P-val | CRT (N = 104) | No CRT (N = 90) | P-val |
| Post-recovery Visit | 663 +/- 19 | 663 +/- 19 | - | 720 +/- 31 | 720 +/- 31 | - |
| 3 Months | 651 +/- 31 | 681 +/- 32 | 0.479 | 685 +/- 55 | 743 +/- 60 | 0.463 |
| 6 Months | 658 +/- 40 | 738 +/- 41 | 0.143 | 681 +/- 75 | 827 +/- 79 | 0.163 |

**Table 10. Mean Heart Rate Results (Sheet 1 of 2)**

| Heart Rate (bpm) | All Patients | | | NYHA Class III/IV | | |
|---|---|---|---|---|---|---|
| | CRT (N = 240) | No CRT (N = 233) | P-val | CRT (N = 113) | No CRT (N = 101) | P-val |
| Post-recovery Visit | 72.3 +/- 0.6 | 72.3 +/- 0.6 | - | 74.5 +/- 1.0 | 74.5 +/- 1.0 | - |

**Table 10. Mean Heart Rate Results (Sheet 2 of 2)**

| Heart Rate (bpm) | All Patients | | | NYHA Class III/IV | | |
|---|---|---|---|---|---|---|
| | CRT (N = 240) | No CRT (N = 233) | P-val | CRT (N = 113) | No CRT (N = 101) | P-val |
| 3 Months | 70.8 +/- 0.8 | 72.1 +/- 0.8 | 0.20 | 74.1 +/- 1.2 | 73.9 +/- 1.3 | 0.94 |
| 6 Months | 69.4 +/- 1.0 | 70.2 +/- 1.0 | 0.58 | 70.6 +/- 1.6 | 72.5 +/- 1.6 | 0.40 |

## EASYTRAK Lead and System Effectiveness

It was hypothesized that the upper tolerance limit of the chronic left ventricular pacing threshold of the EASYTRAK lead be less than 5.5 V to ensure that an adequate safety margin exists. Chronic left ventricular pacing thresholds shown in Figure 7 are well within this limit.

All patients implanted with an EASYTRAK lead at first implant, N = 443

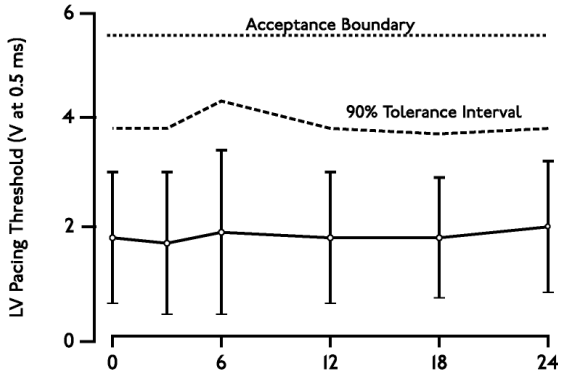


**Figure 7. EASYTRAK lead threshold measurements**

| Statistic[a] | Implant | 3 Months | 6 Months | 12 Months | 18 Months | 24 Months |
|---|---|---|---|---|---|---|
| N | 435 | 347 | 330 | 233 | 103 | 25 |
| Mean +/- SD | 1.8 +/- 1.2 | 1.7 +/- 1.3 | 1.9 +/- 1.5 | 1.8 +/- 1.2 | 1.8 +/- 1.1 | 2.0 +/- 1.2 |
| Range | 0.2 - 7.5 | 0.2 - 7.5 | 0.2 - 7.5 | 0.4 - 7.5 | 0.6 - 7.5 | 0.6 - 5.0 |
| Upper Tolerance Limit | 3.8 | 3.8 | 4.3 | 3.8 | 3.7 | 3.9 |

a. EASYTRAK lead models: 4511, 4512, and 4513.

Mean chronic biventricular R-wave amplitudes are measured as a combination of the R-waves from both the right ventricle (commercially available ENDOTAK lead) and left ventricle (EASYTRAK lead). It was hypothesized that the mean biventricular

R-wave amplitude be greater than 5 mV to ensure proper sensing. In Figure 8, the performance of the EASYTRAK lead system was significantly above this value ($p < 0.01$).

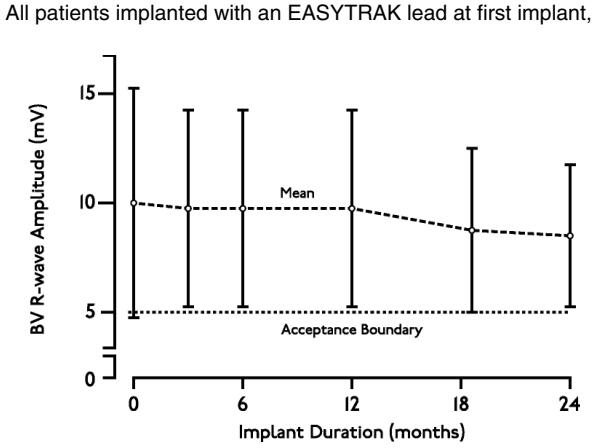


**Figure 8. EASYTRAK biventricular-sensed R-wave amplitude**

| Statistic | Implant | 3 Months | 6 Months | 12 Months | 18 Months | 24 Months |
|---|---|---|---|---|---|---|
| N | 433 | 346 | 326 | 220 | 99 | 23 |
| Mean +/- SD | 10.0 +/- 5.2 | 9.9 +/- 4.4 | 9.9 +/- 4.5 | 9.8 +/- 4.4 | 8.9 +/- 3.5 | 8.5 +/- 3.3 |
| Range | 1.9 - 25.0 | 1.4 - 25.0 | 1.7 - 25.0 | 1.2 - 25.0 | 2.6 - 20.4 | 2.2 - 13.6 |

The impedance measured by the CONTAK CD device is the parallel combination of the left ventricular (EASYTRAK) and right ventricular (ENDOTAK) leads simultaneously. Therefore, the biventricular lead impedance will be substantially less than that of either lead alone. It was hypothesized that the lower limit of the 95% confidence interval of the mean chronic biventricular lead impedance would be greater than 200 Ω to ensure proper pulse generator function. The lower limit of the 95% confidence interval of the chronic biventricular lead impedance exceeds this value (Figure 9).

All patients implanted with an EASYTRAK lead at first implant, N = 443

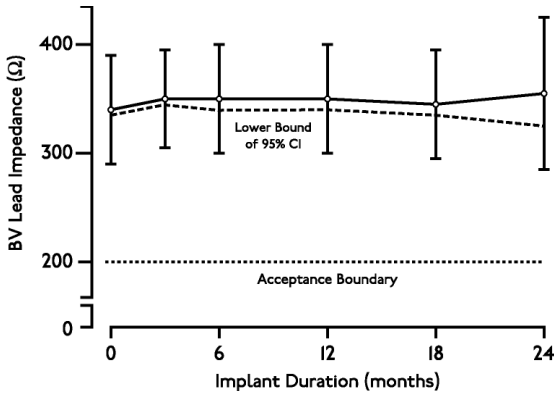


**Figure 9. EASYTRAK biventricular pacing impedance**

| Statistic | Implant | 3 Months | 6 Months | 12 Months | 18 Months | 24 Months |
|---|---|---|---|---|---|---|
| N | 436 | 355 | 336 | 237 | 107 | 26 |
| Mean +/- SD | 340 +/- 46 | 352 +/- 47 | 349 +/- 50 | 351 +/- 51 | 347 +/- 46 | 356 +/- 67 |
| Range | 243 - 550 | 248 - 519 | 186 - 534 | 237 - 513 | 254 - 507 | 267 - 520 |
| 95% CI | (336, 344) | (347, 357) | (344, 355) | (345, 358) | (338, 356) | (329, 383) |

## EASYTRAK Lead Placement Success Rate

The EASYTRAK lead was implanted in 448/517 (87%) of patients who underwent the implant procedure. Table 11 shows the reasons for inability to place the EASYTRAK lead. Table 12 provides the EASYTRAK lead implant success rate.

**Table 11. Reasons for Unsuccessful EASYTRAK Lead Implant**
(Patients with unsuccessful attempt to implant EASYTRAK lead, N = 69)

| Reason | # of pts | % |
|---|---|---|
| Inability to locate or cannulate the coronary sinus | 29 | 42 |
| Dislodgment of EASYTRAK lead while removing guide catheter | 13 | 18.8 |
| Inability to advance the lead to a stable position | 11 | 15.9 |
| Inability to obtain adequate pacing thresholds | 6 | 8.7 |
| Procedure stopped due to coronary sinus dissection or perforation | 5 | 7.2 |

**Table 11. Reasons for Unsuccessful EASYTRAK Lead Implant**
(Patients with unsuccessful attempt to implant EASYTRAK lead, N = 69)

| Reason | # of pts | % |
|---|---|---|
| Procedure stopped due to transient AV block | 1 | 1.4 |
| Procedure stopped due to venous perforation during subclavian stick | 1 | 1.4 |
| Reason not stated | 1 | 1.4 |
| Extracardiac stimulation | 1 | 1.4 |
| Inability to place an atrial pace/sense lead | 1 | 1.4 |
| **Total** | **69** | **100** |

**Table 12. Lead Placement Success Rate**
(All patients implanted or attempted with EASYTRAK lead, N = 517)

| Measurement | All Procedures |
|---|---|
| Number of patients implanted or attempted | 517 |
| Number of placements[a] of the EASYTRAK Lead | 448 |
| Rate | 87% |
| 95% CI | (84%, 90%) |

a. Defined as an EASYTRAK implant procedure that is concluded with the implant of the investigational cardiac resynchronization system.

Although some situations such as patient anatomy and poor thresholds cannot be avoided, increased investigator experience with the EASYRAK lead and accessories was associated with improved success, decreased total procedure time (measured skin-to-skin), and decreased fluoroscopy exposure time (Figure 10).

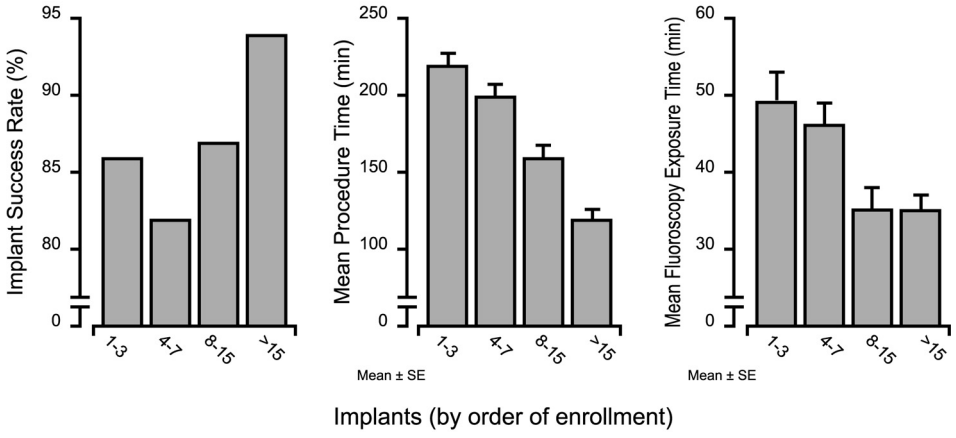


**Figure 10. EASYTRAK success rate, procedure time, and fluroscopy exposure time.**

## Biventricular Antitachycardia Pacing (ATP) Conversion Effectiveness Performance

The conversion rate of induced monomorphic ventricular tachycardia (MVT) was 64% and that of spontaneous MVT was 88%.

### *Ventricular Tachyarrhythmia Detection Time*

The VENTAK CHF and CONTAK CD devices sense events from both ventricles simultaneously. Ventricular tachyarrhythmia detection time was analyzed to determine if the additional lead had an adverse effect on sensing VT/VF. Guidant's ICDs typically have a detection time of two seconds. The VF detection time of 2.1 ± 0.6 seconds was statistically significantly lower than 6 seconds[1] ($p < 0.01$), demonstrating that there was no statistically significant prolongation of induced VF detection times with the additional left ventricular lead. There were also no adverse events reported in which a VENTAK CHF or CONTAK CD failed to detect a spontaneous ventricular tachyarrhythmia.

## EASYTRAK Lead and System Safety

### *EASYTRAK Lead Safety*

Safety was established using the rate of adverse events that are either related to the EASYTRAK lead or to the implant procedure necessary to place the EASYTRAK lead.

An EASYTRAK lead implant procedure was performed in 517 patients with 448 patients (86.7%) being successfully implanted with the EASYTRAK lead.[2] The upper boundary of the 95% confidence interval was hypothesized to be less than 23% at six months (Table 13).

**Table 13. Lead-Related Adverse Events at Six Months**

| Patient Population | N | Event Rate (%) | 95% CI |
|---|---|---|---|
| All Patients | 517 | 12.2 | (9.4, 15.0) |
| NYHA Class III/IV | 201 | 17.4 | (12.7, 22.7) |

1. Detection time at implant with legally marketed Guidant ICD devices is typically two seconds, and investigators have stated that an additional delay of 3 to 5 seconds would be a clinically significant event. The expected detection time is 2 seconds (95% CI: [0, 6 sec]).
2. For purposes of defining event rates, a denominator of 448 will be used for those adverse events that pertain to chronically implanted EASYTRAK leads, and a denominator of 517 will be used for those adverse events that pertain to the implant procedure of the EASYTRAK lead.

Fifty-three lead-related adverse events were reported during the clinical investigation of the EASYTRAK lead among the 448 patients who were implanted with an EASYTRAK lead. Twenty-seven procedure-related adverse events were reported among the 517 patients who underwent the implant procedure for an EASYTRAK lead. The overall lead-related adverse event rate was 14.5% (95% CI [11.5–17.5%]). Table 14 reports lead-related adverse events observed during the CONTAK CD Study.

**Table 14. EASYTRAK Lead-Related Adverse Events Throughout the Study**
(All patients implanted, N=448; All patients attempted, N=517)

| Adverse Events | Total | % of pts (95% CI) |
|---|---|---|
| **Lead-Related, N = 448** | | |
| Loss of capture/lead dislodgment | 31[a] | 6.9 (4.6–9.3) |
| Ventricular oversensing | 11 | 2.5 (1.0–3.9) |
| Extracardiac stimulation | 9 | 2.0 (0.7–3.3) |
| Insulation breach | 2 | 0.4 (0.0–1.1) |
| **Procedure-Related, N = 517** | | |
| Transient AV block | 6 | 1.2 (0.2–2.1) |
| Coronary venous dissection | 5 | 1.0 (0.1–1.8) |
| Coronary venous perforation | 5 | 1.0 (0.1–1.8) |
| Transient renal failure | 5 | 1.0 (0.1–1.8) |
| Pericardial effusion | 2 | 0.4 (0.0–0.9) |
| Finishing wire left in lead | 1 | 0.2 (0.0–0.6) |
| Right ventricular lead dislodgment | 1 | 0.2 (0.0–0.6) |
| Guide wire fracture | 1 | 0.2 (0.0–0.6) |
| Hypotension due to blood loss | 1 | 0.2 (0.0–0.6) |
| **Total (unique patients)** | **75** | **14.5 (11.5–17.5)** |

a. Twenty-six events were successfully corrected in a repeat procedure

The most common of the 53 lead-related adverse events (>1% incidence) included loss of left ventricular capture (31 patients, 6.9%), ventricular oversensing (11 patients, 2.5%), and extracardiac stimulation (9 patients, 2.0%). These events were typically resolved with surgical intervention.

The most common of the 27 procedure-related adverse events (> 1% incidence) included coronary venous trauma (10 patients, 2.0%), transient atrioventricular block (6 patients, 1.2%), and transient renal failure (5 patients, 1.0%). These events were typically resolved without intervention and no permanent long-term sequelae were reported.

## Severe, Device-Related Adverse Events and Operative Mortality

The incidence of severe, device-related events was reported in 7 of 567 patients (1.2%); this was significantly less than the hypothesized rate of 20% ($p < 0.01$) (Table 15). Table 16 reports system, device-related, severe adverse events observed during the CONTAK CD Study.

**Table 15. Adverse Events and Operative Mortality**
(All patients attempted or implanted, N = 567)

| Measurement | N | % | 95% CI |
|---|---|---|---|
| Severe, Device-Related Adverse Events (Type I)[a] | 7 | 1.2 | (0.3, 2.1) |
| All-Cause Operative Mortality (< = 30 Days Post Implant) | 12 | 2.1 | (0.9, 3.3) |

a. Percent is of patients with at least one event.

**Table 16. System, Device-Related, Severe Adverse Events**
(All patients attempted or implanted, N = 567)

| Adverse Event | # of pts | % of pts (95% CI) |
|---|---|---|
| Telemetry difficulty; device explanted | 2 | 0.4 (0.0–0.9) |
| Ventricular tachycardia during CPX testing | 1 | 0.2 (0.0–0.5) |
| Coronary sinus perforation | 1 | 0.2 (0.0–0.5) |
| Inappropriate shock due to oversensing | 1 | 0.2 (0.0–0.5) |
| Lead dislodgment | 1 | 0.2 (0.0–0.5) |
| Anaphylaxis in association with use of a pulmonary artery catheter | 1 | 0.2 (0.0–0.5) |

Operative mortality, defined as death from any cause within 30 days of implant, was reported in 12 of 567 patients (2.1%) undergoing the implant procedure. The outcome is significantly less than the hypothesized rate of 9% ($p < 0.01$). Table 17 reports the cause of death for operative mortality.

**Table 17. Cause of Death for Operative Mortality**
(All patients attempted or implanted, N = 567)

| Cause of Death | Implants N = 501 | Attempts N = 66 | Total N = 567 |
|---|---|---|---|
| Cardiac: pump failure | 5 | 1 | 6 |
| Cardiac: arrhythmic | 2 | 1 | 3 |
| Noncardiac | 2 | 0 | 2 |
| Unknown | 1 | 0 | 1 |
| **Total** | **10** | **2** | **12** |

## System Safety Profile

Analysis of system safety was performed on the complication-free rate of device-related adverse events, regardless of whether or not they were related to the investigational device (Figure 11). Table 18 outlines the device related complications. This study used an acceptance criterion such that the lower boundary of the 95% confidence interval could not be less than 70%.

**Table 18. Device-Related Complications[a]**
(All patients implanted, N = 448; All patients attempted, N = 517)

| Complication | # of pts | % of pts |
|---|---|---|
| **All patients implanted (N = 448)** | | |
| Loss of LV capture | 31 | 6.9 |
| Loss of right atrial capture | 7 | 1.6 |
| Ventricular oversensing | 6 | 1.3 |
| Extracardiac stimulation | 5 | 1.1 |
| **All patients attempted or implanted (N = 517)** | | |
| Infections | 7 | 1.4 |

a. This table represents patients attempted or implanted with the EASYTRAK lead; most common (> 1%) device-related complications reported.

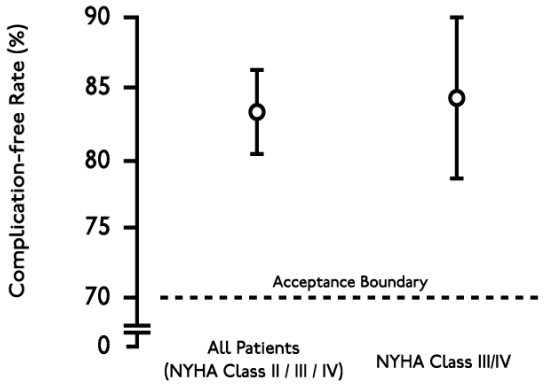


**Figure 11. System safety.**

System safety for the All Patients group and NYHA Class III/IV subgroup as determined by the device-related complication-free rate was within the 70% acceptance boundary for safety.

## Verification of CRT Delivery

The delivery of biventricular pacing throughout the CONTAK CD Study was confirmed by comparing the programmed device output to the biventricular pacing threshold and demonstrating that capture was maintained in daily activities and during exercise.

The investigational plan recommended programming the device output to at least twice the biventricular pacing voltage threshold. Electrocardiograms (ECGs) from Holter Monitors during daily activities were received and analyzed to verify that total capture was maintained at the 3-month and 6-month visits and to ensure that the safety margin was adequate. Cardiopulmonary exercise tests (CPX) were performed on patients who were randomized to receive CRT therapy at 3- and 6- month visits.

- In 623 evaluations of safety margin at baseline, three-, and six-months, the device output was programmed to deliver a voltage approximately three times that necessary to stimulate both ventricles.

- A total of 1139 Holter monitors were placed throughout the study at baseline, three-, and six-months. The tests indicated only 4 instances (0.4%) of inappropriate pacing or sensing that were all corrected with device programming.

- A total of 316 CPX tests at the three- and six-month follow-up visits were performed in patients with CRT who also had interpretable ECG results. Of these, 277 (88%) had continuous CRT delivery throughout exercise. The remaining 39 patients (12%) had continuous CRT delivery until the sinus rate exceeded the maximum tracking rate (MTR).

## Focused Confirmatory Study

### Study Design

The Focused Confirmatory Study (FCS) was a prospective, multicenter study conducted in the United States in 127 patients who participated in an exercise performance study. The purpose of the FCS was to confirm effectiveness results related to functional capacity measures, specifically the Peak $VO_2$ and 6-Minute Hall Walk, previously reported in the NYHA Class III/IV subgroup of the CONTAK CD Study.

CRT was provided in the same manner for the FCS as for the CONTAK CD Study. The EASYTRAK lead, along with market approved right atrial and right ventricular leads were used to provide biventricular stimulation.

## Study Patients

The patients in the FCS had the same heart failure indications as the patients in the NYHA Class III/IV subgroup of the CONTAK CD Study; i.e., patient inclusion criteria included NYHA Class III or IV while on drug therapy, QRS duration ≥ 120 ms, and Left Ventricular Ejection Fraction (LVEF) ≤ 35%.

A baseline physical assessment and functional measures were performed prior to CRT system implant. Patients were eligible for participation in the study if they were capable of walking between 150 and 425 meters. In addition to a Six-Minute Walk test, other special tests were performed prior to implant consisting of a symptom-limited treadmill test and completion of the Minnesota Living with Heart Failure Questionnaire to assess Quality of Life. CRT therapy was enabled immediately upon device implant. Patients were followed at one week, one month, three months, six months and every three months thereafter for a routine physical assessment and device evaluation. Special testing as defined above was repeated at three months and six months post-implant.

Prior to study entry, patients were stable on optimal heart failure medications (ACE inhibitors or substitute > 1 month and beta blockers > 3 months). Patients were excluded if they were indicated for either a pacemaker or ICD or if they were hospitalized for heart failure in the month prior to enrollment.

## Baseline Demographics

The patient characteristics at study entry are summarized in Table 19.

**Table 19. Preimplant Characteristics of Study Patients (N = 127)**

| Characteristics | All Patients Receiving CRT | Characteristic | All Patients Receiving CRT |
|---|---|---|---|
| Age (years) | 61 ± 12 | QRS width (ms) | 159 ± 27 |
| Male Gender (%) | 69 | LBBB/NSIVCD (%) | 91 |
| NYHA Class III (%) | 94 | Heart failure medications (%) | |
| Ischemic Etiology (%) | 49 | • ACE inhibitor or ARB | 91 |
| LVEF (%) | 23 ± 7 | • Beta blockers | 77 |
| Resting heart rate (bpm) | 73 ± 12 | • Digoxin | 76 |
| | | • Diuretics | 98 |

## Inclusion Criteria

Inclusion criteria included:

- Moderate or severe heart failure, defined as symptomatic heart failure for at least six months with NYHA Class III or IV symptoms at the time of enrollment, AND at least one of the following events in the previous 12 months:
  - — Hospitalization for heart failure management
  - — Outpatient visit in which intravenous (IV) inotropes or vasoactive infusion were administered continuously for at least 4 hours
  - — Emergency room visit of at least twelve hours duration in which IV heart failure medications were administered (including diuretics)
- QRS ≥ 120 ms and PR interval > 150 ms from any two leads of a 12-lead ECG
- Left ventricular ejection fraction ≤ 35%
- Left ventricular end diastolic dimension ≥ 60 mm (required only if LVEF measured by echo)
- Age ≥ 18 years
- Optimal pharmacologic therapy for heart failure
- Able to walk between 150 and 425 m in a Six-Minute Walk test

## Major Differences Between CONTAK CD and Focused Confirmatory Study Patients

The CONTAK RENEWAL family of CRT-Ds and CONTAK CD devices provide the same cardiac resynchronization therapy (biventricular pacing) and have the same Indications for Use.

Therefore, the CONTAK CD clinical trial data used to support CONTAK CD is also applicable to all Guidant/Boston Scientific CRT-Ds including the LIVIAN. The primary difference between CONTAK CD devices and CONTAK RENEWAL family of CRT-Ds is that CONTAK CD utilizes an electrically common RV and LV sensing/pacing circuit whereas CONTAK RENEWAL family of CRT-Ds incorporate an independent RV and LV sensing/pacing circuit. Additional clinical analysis was also conducted with CONTAK RENEWAL to provide confirmation that the independent sensing and pacing capability did not adversely affect the ability of the device to detect ventricular tachyarrhythmias or provide continuous biventricular pacing therapy.

Some of the major differences between the study populations included:

- Patients were excluded from the FCS if they were indicated for either a pacemaker or implantable cardioverter defibrillator (ICD). Patients in the CONTAK CD Study were excluded if they met the indications for a pacemaker; however, they were required to meet the general indications for an ICD.

- Patients were excluded from the FCS if they were hospitalized for heart failure in the month prior to enrollment; whereas, there was no exclusion for hospitalization for heart failure in the month prior to enrollment for the CONTAK CD patients.

- Patients in the FCS must have been on stable, optimal heart failure medications, including beta blocker therapy for three months, prior to study entry. Patients in the CONTAK CD Study could be optimized on drug therapy between the time from device implant until the treatment phase (either CRT or No CRT) began.

- Patients in the FCS had baseline measurements performed prior to implant. Patients in the CONTAK CD Study had baseline measurements performed post-implant, but before programming of the randomized therapy.

- Seventy-seven percent of patients in the FCS (98 of N = 127) were on beta blockers compared to 42% in the CONTAK CD Study (95 of N = 227).

- Forty-nine percent of the patients in the FCS (62 of N = 127) had ischemic etiology compared to 68% in the CONTAK CD Study (154 of N = 227).

## Endpoints

The primary endpoints of the study were Peak $VO_2$ and Six-Minute Walk distance. The study was designed to show a mean change of at least 1ml/kg/min and a 95% lower confidence bound (LCB) at least 0.5 ml/kg/min. The study was also designed to detect a statistically significant improvement in the Six-Minute Walk distance at a one-sided significance level of 0.10. Additionally, two ancillary analyses of Quality of Life Score and NYHA Class had to demonstrate a change that was directionally favorable towards CRT using descriptive statistics.

## Study Results

### *Peak $VO_2$*

A statistically significant improvement from baseline of 0.94 ± 0.30 ml/kg/min with a 95% LCB of 0.45 was observed in Peak $VO_2$ after six months of CRT.

### *Six-Minute Walk*

Statistically significant improvements versus baseline were observed in Six-Minute Walk distance after six months of CRT with an observed mean improvement of 50.9 ± 10.4 m with a 95% LCB of 37.6 m.

### *Quality of Life*

Consistent with the other analyses, a statistically significant improvement of 23.9 ± 2.6 points was observed in the Quality of Life score after six months of CRT with a 95% LCB of 19.7 points.

### *New York Heart Association Class*

After six months of CRT, a statistically significant improvement in NYHA Class was observed with 60.4% of patients improving one or more NYHA Class.

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