



Expanded Indications for Boston Scientific's CRT-D Devices Based on MADIT-CRT Study

FDA Review of P010012 / S230

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March 18, 2010

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Proposed Indications

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

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

Benefits & Risks

Potential Benefits

- Reduction in heart failure events including hospitalizations
- Reduction in all-cause mortality

Potential Risks

- AE's related to chronic implantation of LV lead
- AE's related to implant procedure for LV lead

Device-Based Therapy

MADIT-CRT patients already satisfy the evidence-based indications for ICD therapy.

MADIT-II

- NYHA Class I patients with ischemia and a LVEF $\leq 30\%$

SCD-HeFT

- NYHA Class II patients with or without ischemia and a LVEF $\leq 30\%$

Based on MADIT-CRT, which system is indicated for these patients?

ICD or CRT-D

Primary Discussion Points

- Characteristics of enrolled patients
- Interpretation of clinical study results
- Evaluation of risks and benefits
- Potential biases during study
- Limitations of sponsor's statistical analyses
- Plans for post-approval study

FDA Presentations

- Kim Selzman – Clinical
- Laura Thompson – Statistical
- Shaokui Wei – Epidemiology
- Ken Skodacek – Conclusions



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Outline

- Overview of Cardiac Resynchronization Therapy
- Overview of MADIT-CRT Trial
- Baseline Characteristics of Enrolled Subjects
- Primary Effectiveness Endpoint
- Sub-Group Analyses
- Primary Safety Endpoint
- Incremental Risks of CRT-D Therapy
- Overall Mortality
- Summary

Cardiac Resynchronization Therapy

- Synchronized biventricular pacing has been shown to reduce morbidity and mortality in NYHA Class III-IV heart failure patients with an LVEF $\leq 35\%$ and a QRS duration $\geq 120\text{ms}$
- Current FDA-approved indication for BSC CRT-D is restricted to these patients who remain symptomatic despite optimal drug therapy
- CRT is not FDA approved for NYHA Class I-II patients
- MADIT-CRT enrolled NYHA Class I-II patients with an LVEF $\leq 30\%$ and a QRS $\geq 130\text{ ms}$

Overview of MADIT-CRT Trial

Study Design	Randomized, controlled
Blinding	Patients and investigators unblinded Heart Failure Event Committee blinded
Randomization	3:2 (CRT-D:ICD)
Analysis	Intention-to-treat
Enrollment Criteria	NYHA Class I (ischemic only) or Class II (all) QRS \geq 130 ms and LVEF \leq 30% BB, ACE-I/ARB drug therapy stable for 1 month
Enrolling Sites	110 total sites 87 US sites, 23 outside the US (OUS)

Baseline Characteristics

Characteristic	ICD (n=731)	CRT-D (n=1089)
Beta Blocker (goal, taking)*	28%, 93.2%	30%, 93.3%
NYHA Class I	15.5%	14%
QRS Duration ≥ 150 ms	65.1%	64.2%
Left Bundle Branch Block	71.3%	69.9%
6MWT (m)	363 \pm 108	358 \pm 106
Prior HF Hospitalization	36.7%	38.8%
Prior NYHA III-IV (>3 months prior)	10.4%	10.4%

**Target dose = Carvedilol 50 mg/day or the equivalent dose of another BB*

Beta Blocker Dose at Baseline and during Follow-up

- Beta blocker doses were similar at baseline
- Beta blocker doses increased in the CRT-D group over 3 years of follow up

Time	At or Above Target Dose*		Mean Daily Dose (mg/day)	
	ICD	CRT-D	ICD	CRT-D
Baseline	28%	30%	28 ± 20	28 ± 19
12 months	32%	38%	30 ± 20	33 ± 19
24 months	34%	42%	31 ± 20	34 ± 20
36 months	35%	47%	33 ± 21	36 ± 21

*Target dose = Carvedilol 50 mg/day or equivalent dose of another BB

Potential Consequences of a Unblinded Study Design

- Greater doses of BB for CRT-D patients
 - No concern for bradycardia in CRT-D patients who are pacing 100% of the time
 - Ongoing concern for bradycardia which necessitates RV pacing in ICD patients
- HF medication changes as an outpatient or during a hospitalization
- Considerable number of cross-overs ICD→CRT-D
- ICD subjects withdrew from the trial more frequently than CRT-D subjects

Definition of Heart Failure Event

- Patient with symptoms and/or signs consistent with heart failure in an in-patient or out-patient setting and receiving either
 - IV decongestive therapy (IV diuretics, nesiritide, inotropes) that did not involve formal in-patient hospital admission regardless of the setting
- or
- An augmented HF regimen with oral or IV medications during an in-hospital stay

Crossovers and Other Deviations

	ICD (n=731)	CRT (n=1089)	All Patients (n=1820)
Did not undergo procedure (<i>Intent</i> s)	19 (3%)	10 (1%)	1.6%
Procedure attempted (<i>Attempt</i>)	0% (0)	0.1% (1)	0.1%
Explant / deactivation	1.4% (10)	1.9% (21)	1.7%
Crossover to other therapy	12.9% (94)	8.3% (90)	10.1%

Primary Effectiveness Endpoint: All-Cause Mortality or HF event

Event Types	% of Patients in Treatment Group		Unadjusted Hazard Ratio (95% CI)
	ICD	CRT-D	
Patients with Primary Endpoint Event	26%	17%	0.65 (0.52, 0.80)
Patients with All-Cause Mortality at Any Time	7%	7%	1.01 (0.70, 1.46)
Patients with HF Event	23%	14%	0.58 (0.46, 0.73)
Inpatient HF Event	19%	13%	
Outpatient HF Event	4%	1%	

Secondary and Tertiary Endpoints

Secondary

- Multiple Recurrent heart failure events (HR=0.67 CI 0.53-0.86)

Tertiary

- Echocardiographic Structure and Function (LVESV, LVEDV, LVEF)
 - NYHA Class
 - BNP association with outcome
 - BNP levels
 - Holter recorded parameters (QRS duration) and hemodynamic benefit
-
- All-cause mortality
 - Appropriate defibrillator therapy
 - Quality of life
 - Mitral regurgitation
 - Functional capacity

Sub-Group Analyses

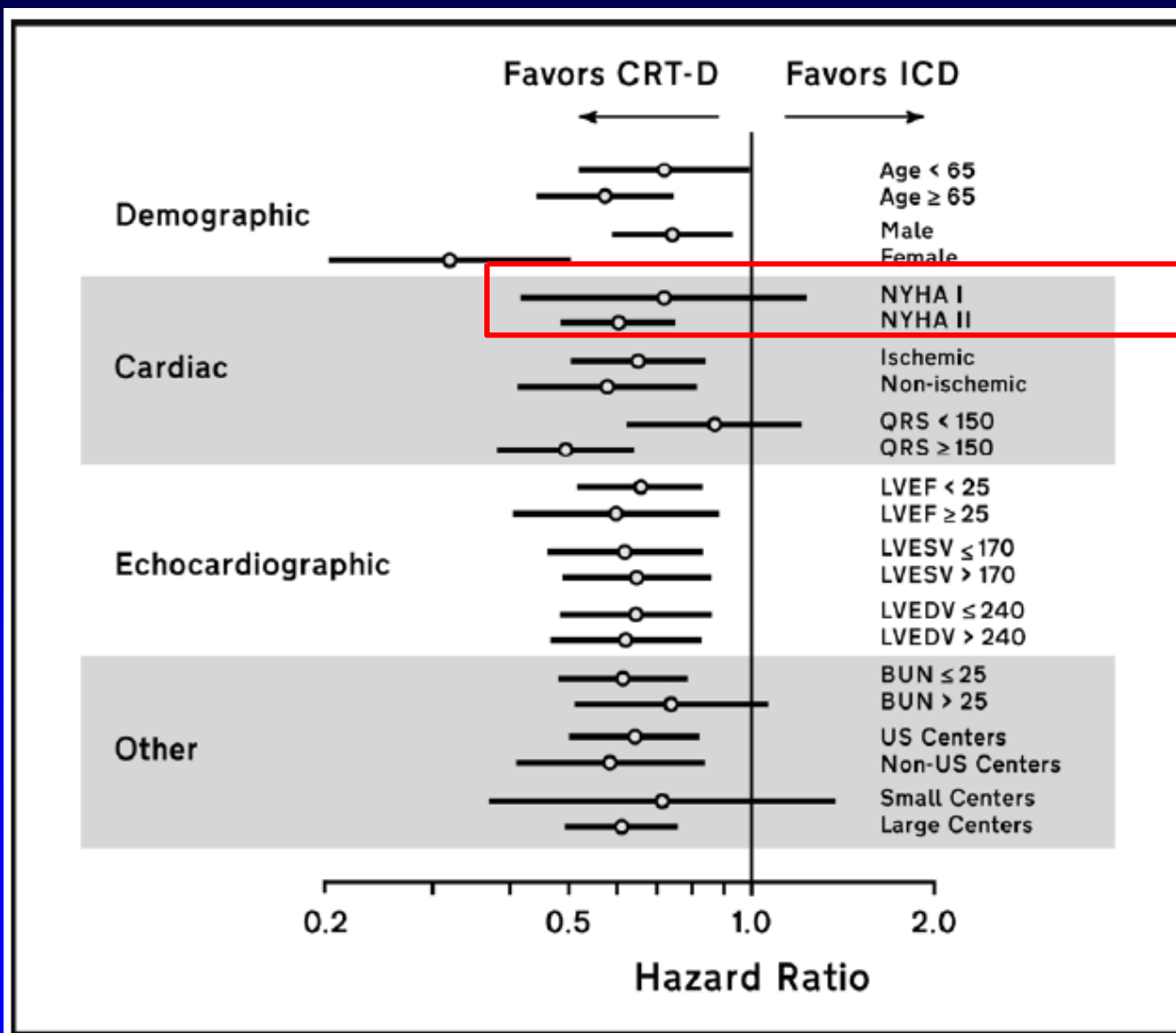
- NYHA Class I and Class II
 - QRS duration <150 ms and ≥ 150 ms
 - Gender
-
- Prior Heart Failure Hospitalizations
 - Previous NYHA Class III-IV
-
- Left Bundle Branch Block

NYHA Class I and Class II

Characteristic	ICD	CRT-D
NYHA Class I Ischemic	15.5%	14.0%
NYHA Class II Ischemic	39.4%	41.0%
NYHA Class II Non-Ischemic	45.1%	45.1%

- NYHA Class I patients comprised only 15% of total cohort
- Although similar representation in both arms, overall proportion of NYHA Class I subjects is small

NYHA Class I and Class II: Hazard Ratios



NYHA Class I: Subjects HF Event-Free During Trial



	0 months	12 months	24 months	36 months	48 months
Class I ICD	113	99	65	24	7
Class I CRT-D	152	137	85	36	6

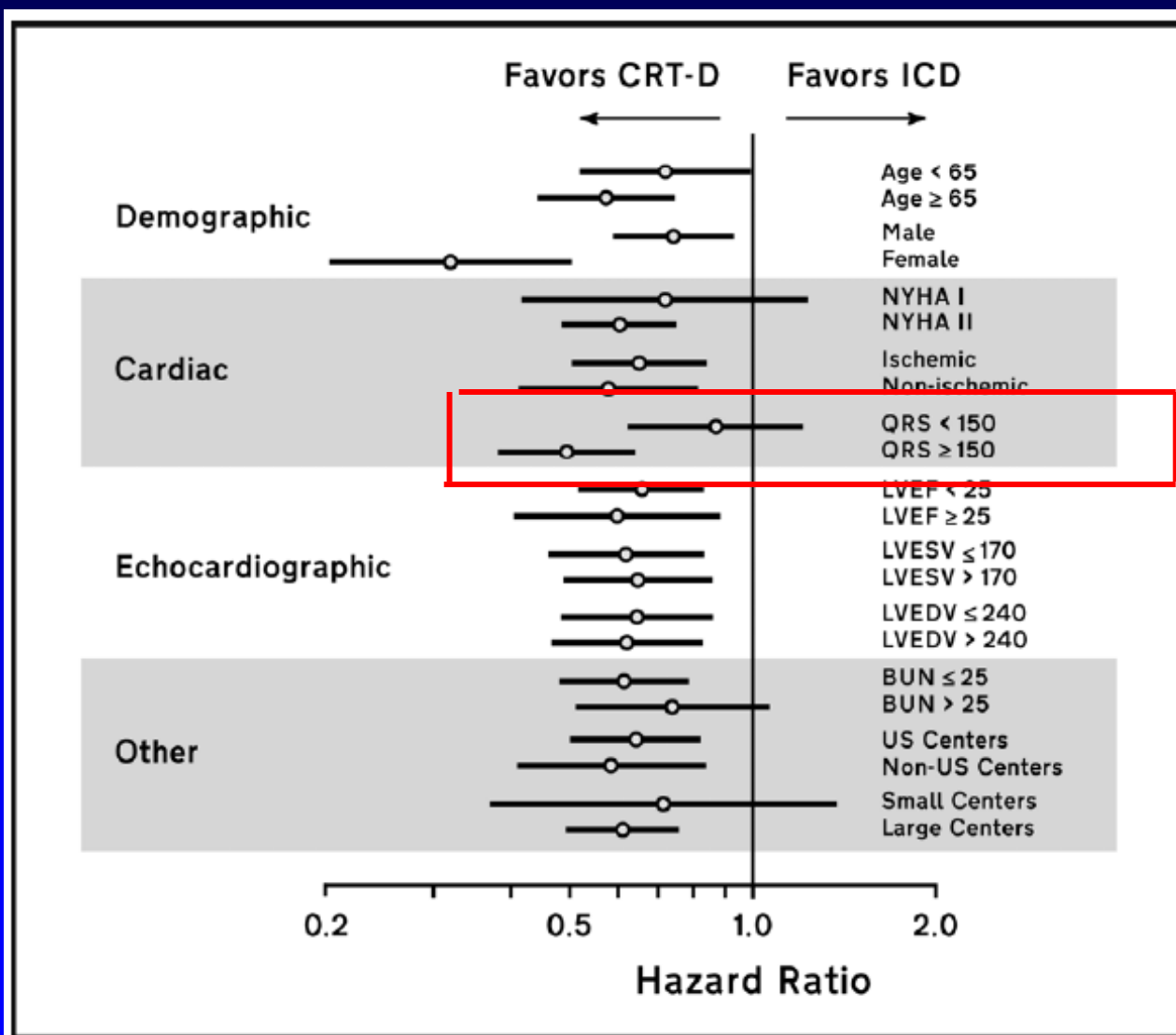
0.2 0.5 1.0 2.0

Hazard Ratio

NYHA Class I and Class II: Additional Differences

- NYHA Class II subjects had a greater prevalence of LBBB and QRS duration ≥ 150 ms
 - LBBB: 73% of Class II, only 54% of Class I
 - QRS ≥ 150 : 67% of Class II, only 52% of Class I
- It is unclear if these differences impact the difference in benefit between groups

QRS Duration $<150\text{ms}$ and $\geq 150\text{ms}$: Hazard Ratios



QRS Duration $<150\text{ms}$ and $\geq 150\text{ms}$: Additional Differences

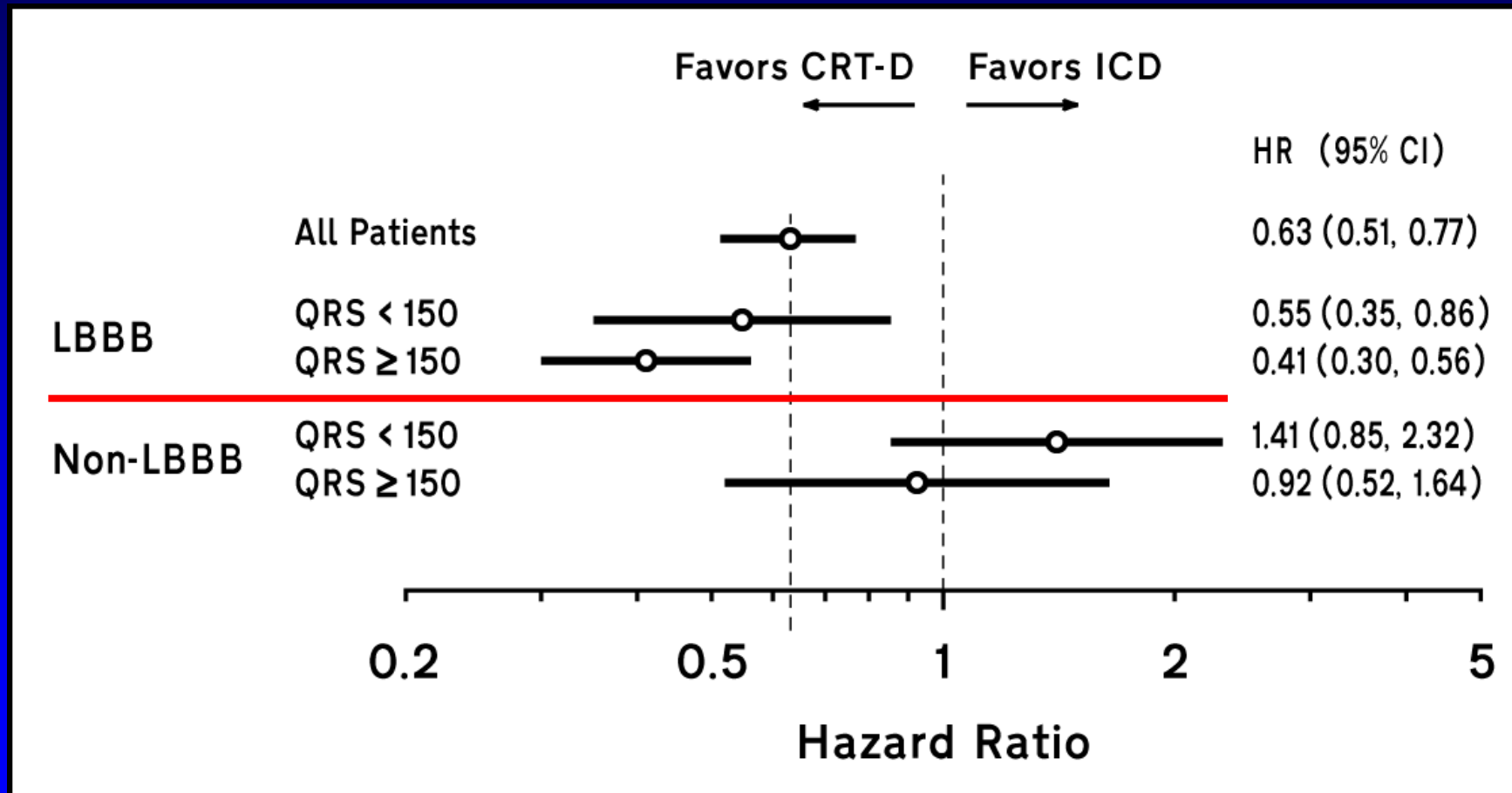
- Subjects with a relatively wider QRS had a greater prevalence of LBBB

	QRS $<150\text{ms}$	QRS $\geq 150\text{ms}$
LBBB	47%	84%

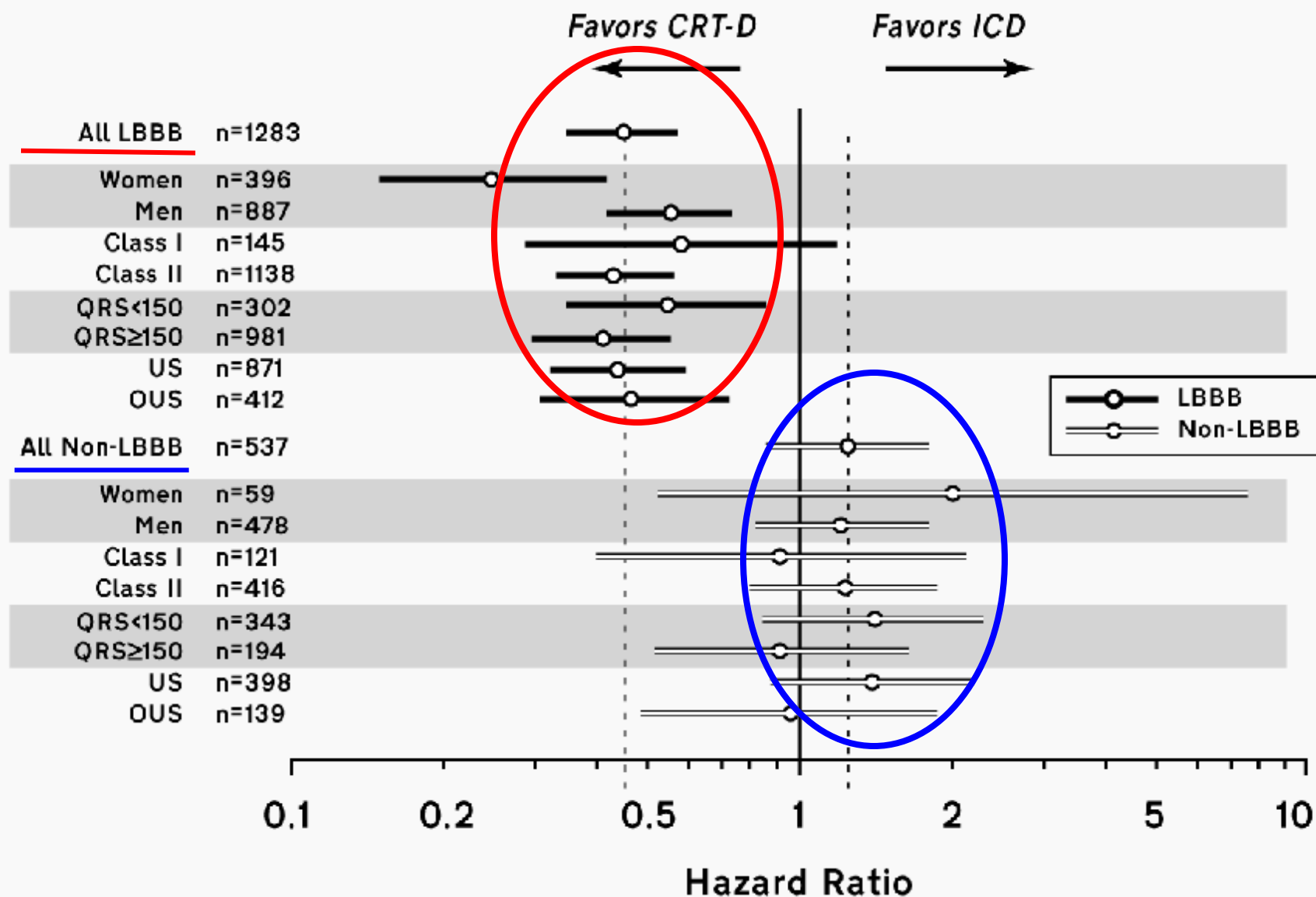
Left Bundle Branch Block

- Although the analysis was post-hoc, the presence of LBBB appears to be a strong factor when determining benefit from CRT-D
- LBBB on EKG represents late activation of the LV
- If the LV is paced, the activation is not delayed
- If the area of greatest activation delay is not the LV free wall, pacing the LV free wall may not improve LV synchrony

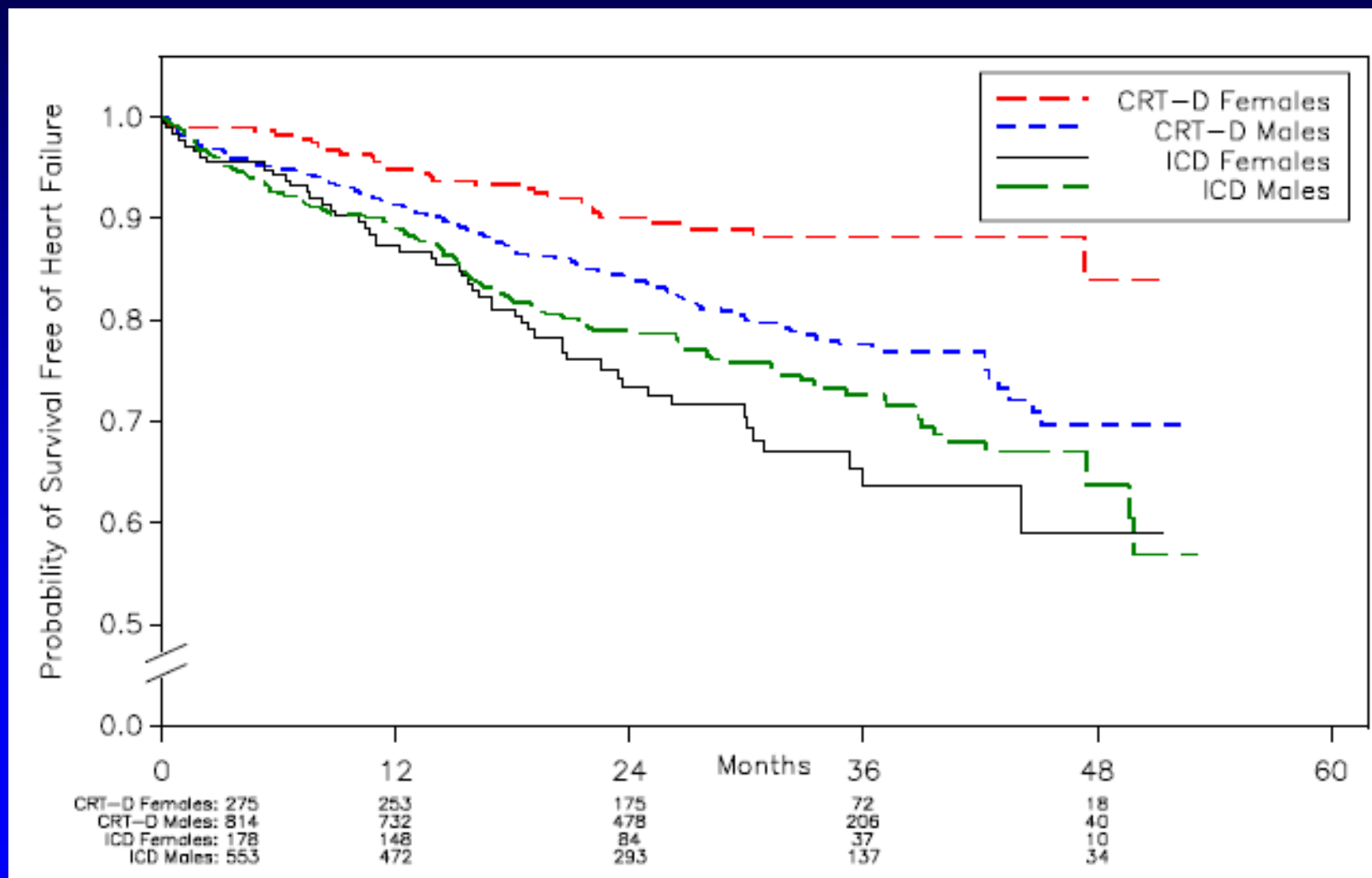
QRS Duration & Bundle Branch Block: Hazard Ratios



Left Bundle Branch Block: Hazard Ratios



Gender: Kaplan-Meier



Gender: Additional Differences

Characteristics of Females compared to Males

- More likely to have prior HFH (44% vs 36%)
- More likely to have LBBB (87% vs 65%)
- More likely to be non-ischemic (72% vs 36%)

Both men and women derived benefit from CRT-D

No difference in complication rate

No clear explanation for gender difference

Prior Heart Failure Hospitalization & Prior NYHA Class III-IV

Previous Heart Failure Event

	HR for time to Event
Prior HFH (37%)	0.72 (0.53, 0.97)
No prior HFH (63%)	0.55 (0.42, 0.73)

Previous NYHA Class III-IV

	HR for time to event
Previously III-IV (10%)	0.73 (0.42, 1.26)
Not Previously III-IV (90%)	0.61 (0.49, 0.76)

- Primary Effectiveness endpoint does not appear to be driven by subjects with prior HFH or prior NYHA Class III-IV

MADIT-CRT Results: Evaluation of Safety

- Overall Mortality
- Primary Safety Endpoint
- Overall System-Related Complications

Overall Mortality and Patient Deaths

- 7% overall mortality
- No difference in mortality between groups
- Leading cause of death: pump failure (40%)
- 127 deaths total
- 9 were classified as device-related, procedure-related, or probably-device related
 - 5 of these were arrhythmic deaths

Procedure and Device Related Deaths in CRT-D Group

- ❖ 6 procedure/device-related deaths
 - 2 implant procedure-related deaths
 - 4 possibly device-related deaths
 - 3 arrhythmic deaths
 - 1 fatal MI in setting of inappropriate shock
- ❖ 6 arrhythmic deaths in CRT-D subjects
 - 2 adjudicated as possibly device-related
 - 4 adjudicated as not device related
- ❖ 1 procedure-related death in ICD group

Primary Safety Endpoint

- Primary Endpoint: CRT-D System-Related Complication-Free rate from implant date to 91 days of follow up
- Performance goal: >70%
- SRC-free rate: 84.8% (82.9% lower CI)
 - 214 SRC in 164 subjects

System Related Complications up to 3-Months: US Sites vs. Outside US Sites

	SRC-Free Rate	
	US sites (US)	Sites Outside of the US (OUS)
Total	87.1%	79.5%
Procedure-Related	94.2%	90.4%
Left Ventricular Lead	94.8%	94.6%
Right Atrial Lead	98.0%	94.0%

Safety Results for Trial Duration

Complication Type	% (number) of CRT-D Patients
Implant Procedure	7.9% (85)
- Pneumothorax	1.5% (16)
Left Ventricular Lead	8% (86)
- Dislodgement	5.8% (63)
- Extracardiac Stimulation	1.3% (14)
- Inability to Capture	0.5% (5)
Pulse Generator	5.9% (64)
- Erosion	0.5% (5)

- 28.5% of CRT-D patients had a procedure or device related complication during the trial
- Most complications occurred in the first 3 months

Incremental Risks: CRT-D Compared to ICD

Complication	% of Patients	
	ICD	CRT-D
Left Ventricular Lead	-	5.2%
Pulse Generator	1.1%	1.5%
Procedure	3.8%	6.9%
Total System-Related Complications	7.5%	15.1%

- Increase in complications in CRT-D group driven by procedure related and left ventricular lead related events
- Increase in pneumothorax and erosion in the CRT-D group

Clinical Summary

- MADIT-CRT met its Primary Effectiveness Endpoint with a reduction in HFE and all-cause mortality from 26% (ICD) to 17% (CRT)
- MADIT-CRT met its Primary Safety Endpoint with a SRC-free rate of 84.8%, with a performance goal of 70%
- CRT-D has an increased complication rate compared to ICD driven largely by LV lead and procedure-related complications
- No difference in all cause mortality demonstrated

Clinical Concerns

- Enrollees were not on target doses of beta blocker medications during the trial
- Limited enrollment of NYHA Class I patients
- Uncertain benefit of CRT in patients without LBBB
- Enrolled subjects may be less healthy than NYHA Class I-II patients in the general clinical setting



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March 18, 2010

Discussion Items

1. Censoring during the trial
2. Crossovers in the trial
3. With an unblinded trial, there is a potential for patient bias as well as physician bias
4. Should device effectiveness be studied further within certain subgroups?

Overview of Study Endpoints

Primary Effectiveness Endpoint

- First occurrence of all-cause mortality or heart failure event (superiority)

Primary Safety Endpoint

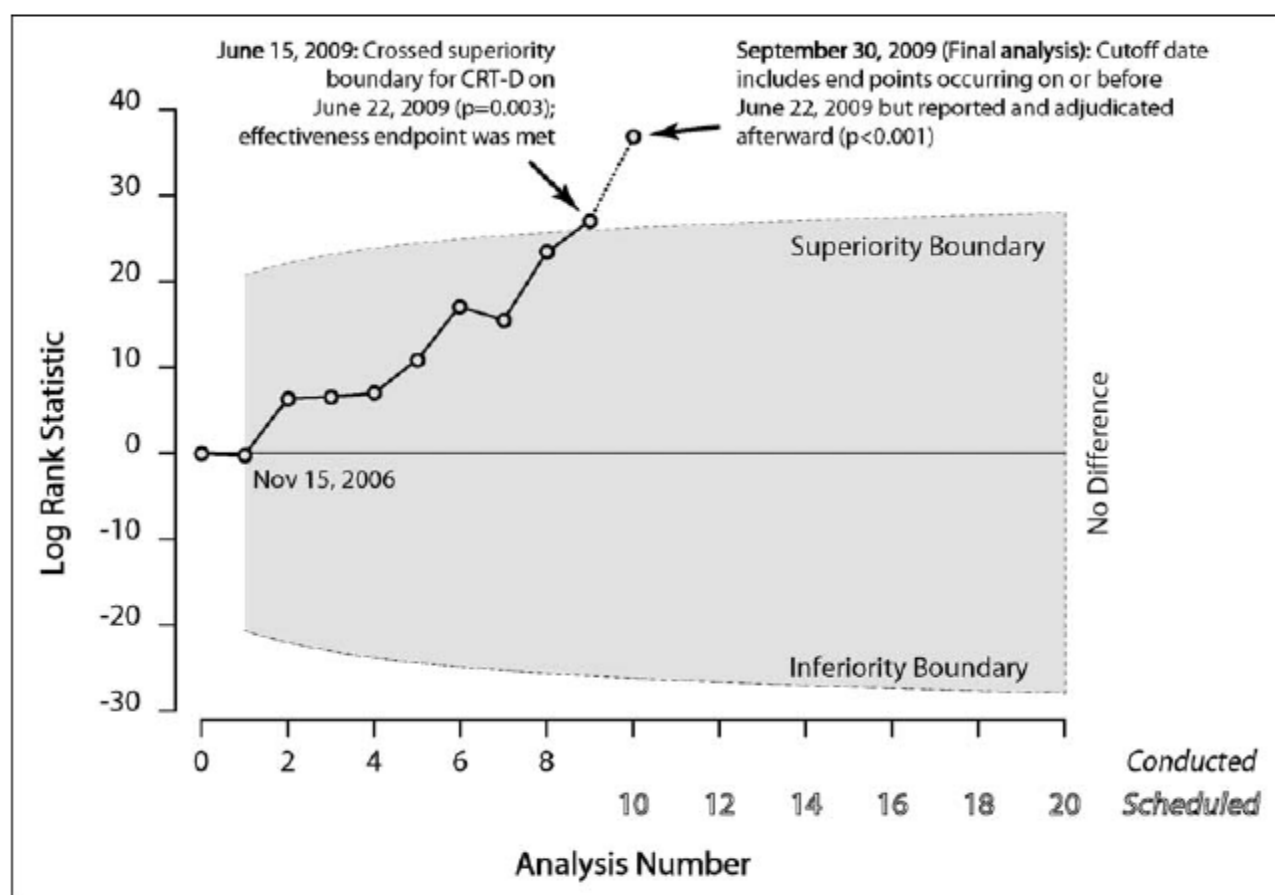
- Rate of system-related complications from CRT-D (single arm)

Primary Effectiveness Endpoint Evaluation: Interim Monitoring

- Group Sequential Design: Wang-Tsiatis design with 20 planned interim looks by a DSMB
 - Overall type I error rate = 0.05
 - (stratified) log-rank statistic was monitored
 - Interim results were not communicated to the sponsor or to investigators until after crossing the superiority boundary.

Primary Effectiveness Endpoint Evaluation: Interim Monitoring

- The statistic crossed the 9th superiority boundary.



Primary Effectiveness Endpoint Evaluation: Interim Monitoring

- When a group-sequential trial is stopped for benefit, the point estimate (HR) may be exaggerated compared to a single-stage study estimate.
- Unadjusted hazard ratios at the stopping point may be biased (for any endpoint).
- Using one method, Sponsor's bias-adjusted HR = 0.66 with adjusted 95% CI (0.52, 0.84)

Discussion Items

1. Censoring during the trial
 2. Crossovers in the trial
- } How robust are conclusions?
3. With an unblinded trial, there is a potential for patient bias as well as physician bias
 4. Should device effectiveness be studied further within certain subgroups?

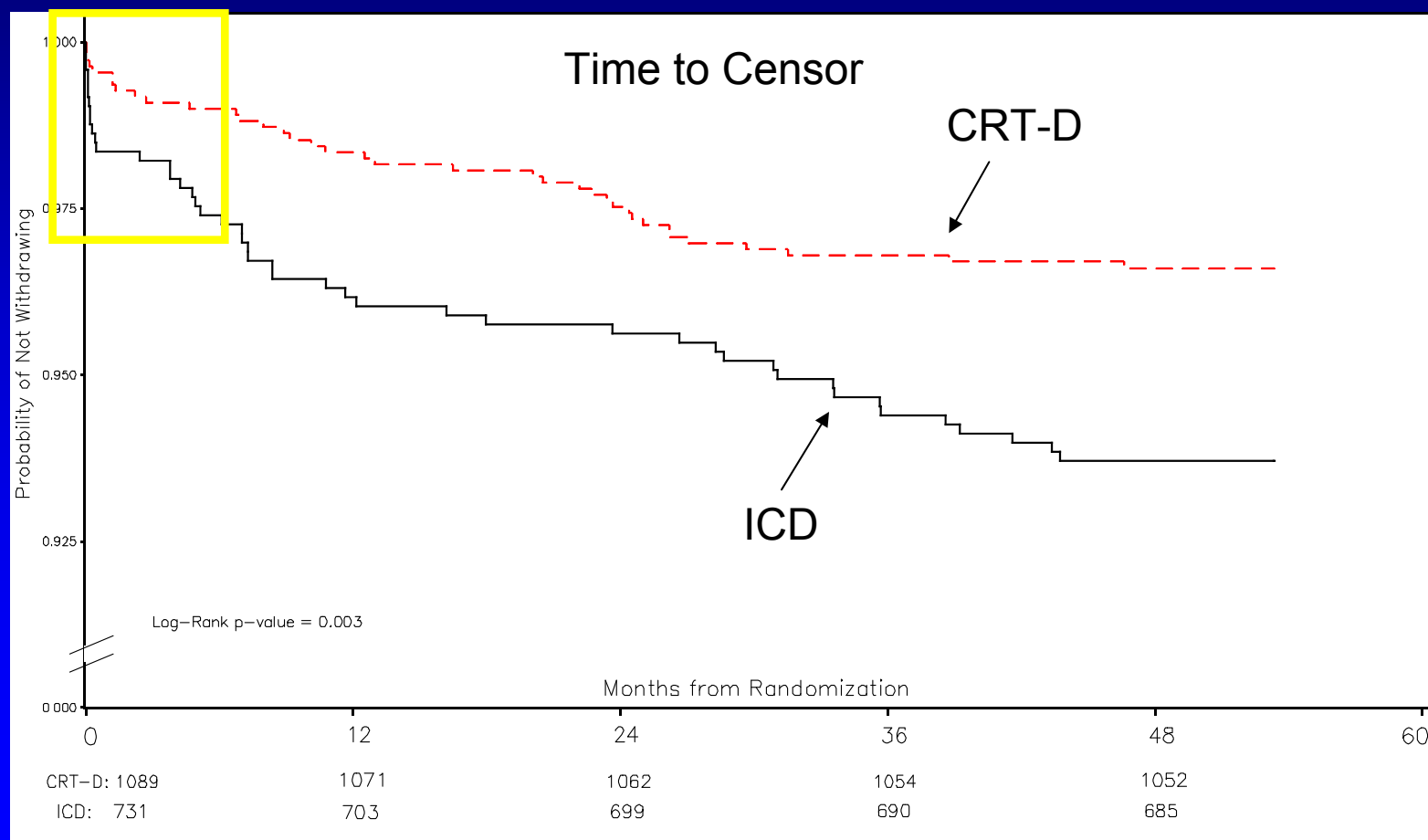
Discussion Item #1: Censoring

- Withdrawals during the trial

	ICD (n=731)	CRT-D (n=1089)
Total	6.3% (46)	3.4% (37)
Not implanted	16	7
Explant	0	4
Unknown?	30	26

Discussion Item #1: Censoring

- Pattern of withdrawals across groups (informative?)

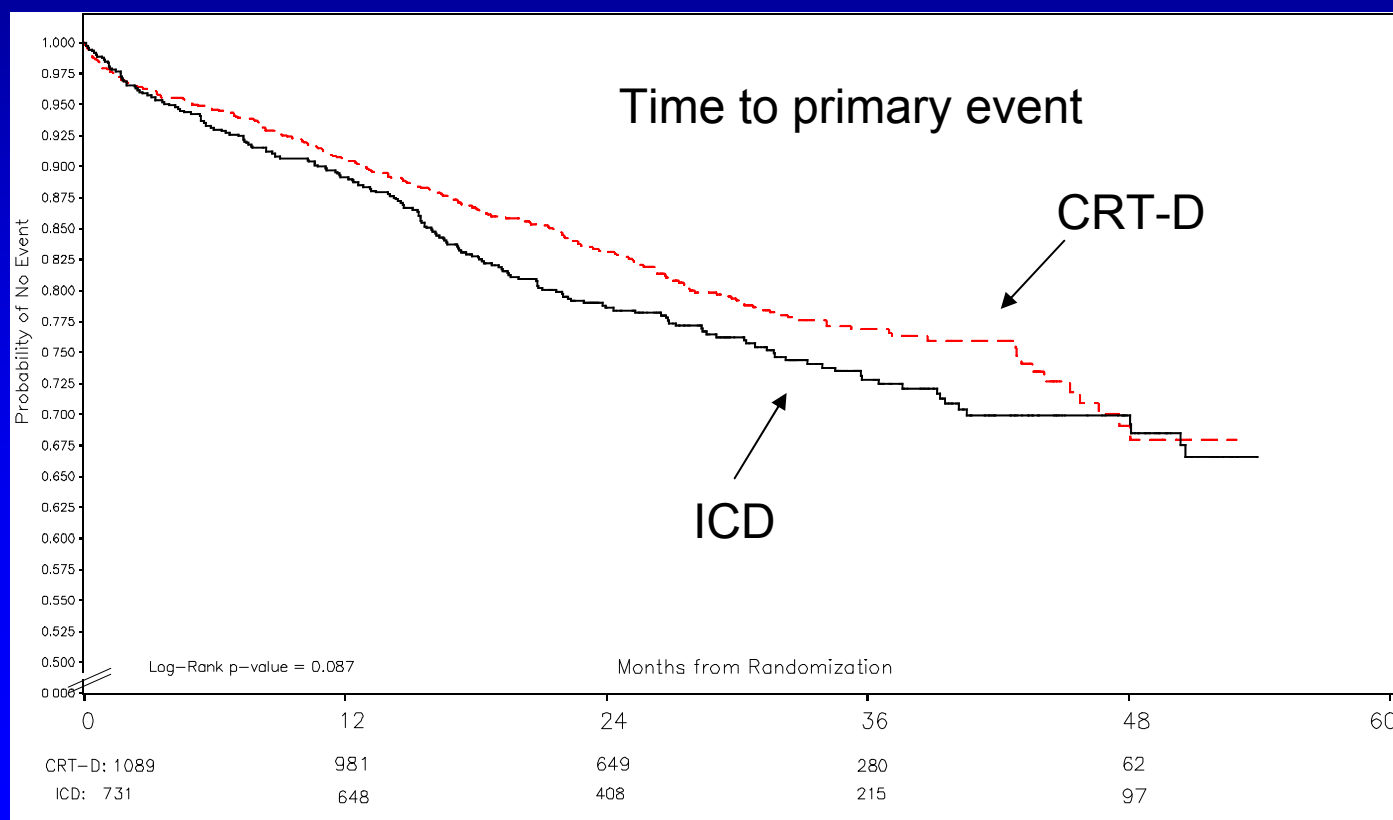


Discussion Item #1: Censoring

- Events classified as “undetermined”
 - 8 ICD; 8 CRT-D with events classified undetermined, who did not withdraw from the trial.
 - 6/8 ICD were assigned “event”
 - 3/8 CRT-D were assigned “event”
- Worst-Case Analysis
 - CRT-D withdrawals and undetermined are assigned events at withdrawal time or time of undetermined event
 - ICD withdrawals and undetermined are censored at maximum recorded follow-up time

Discussion Item #1: Censoring

- Worst-Case Analysis
 - CRT-D are assigned events
 - ICD are censored at maximum recorded follow-up time



Discussion Item #2: Crossovers

- 88 crossed from CRT-D into ICD before event (8% of CRT-D patients)
- 30 crossed from ICD into CRT-D before event (4.1% of ICD patients)
 - 3 patients crossed from ICD into CRT-D, and had an event on day of cross over.

Cumulative crossovers by follow-up time

Group	12 months	24 months	36 months	48 months	> 48 months
CRT-D -> ICD	79	86	86	88	88
ICD -> CRT-D	10	20	27	29	30

Discussion Item #2: Crossovers

- 19 / 88 crossovers into ICD had an event after crossing.
- 9 / 30 crossovers into CRT-D had an event after crossing.
- Primary analysis was as-randomized.
 - The *higher* event rate in patients who crossed into CRT-D was counted against ICD.
 - The *lower* event rate in patients who crossed into ICD was counted toward CRT-D.
- “As-treated” analysis is more conservative, in this case.

Discussion Item #2: Crossovers

- “As-treated” analysis
 - analyze crossovers in their treated groups, not randomized groups (using left truncation up to crossover time)
 - Patients who were not implanted were kept in their randomized groups in order to focus only on treatment switches.
- FDA’s “As-treated” final analysis:
 - Unadjusted HR = 0.66 ; naïve 95% CI (0.53, 0.82)

Discussion Item #3: Blinding of Patients

- Possible consequences when patients are not blinded to their treatment:
 - Not implanted after randomization:
 - 3% ICD; 1% CRT-D.
 - Early withdrawal from the study (before event):
 - Withdrawn < 12 months: 4% ICD; 1.6% CRT-D
- These consequences are preventable by blinding.

Discussion Item #3: Blinding of Physicians

- Possible consequences when physicians are not blinded to treatment assignment:
 - Referral of HF events for adjudication
 - CRT was already approved for NYHA Class III and IV.
 - Physician treatment regarding HF drug administration
 - It is not clear to what extent CRTD benefit was due to beta-blocker dosage increases.
- More “objective” measures such as all-cause mortality do not show device effect

Discussion Item #4: Subgroup Analyses

- A pre-specified, alpha-controlled test of interaction between treatment group and a subgroup on the primary endpoint answers the question:
 - Does the treatment have a different effect across the subgroups? (e.g., in magnitude, direction)
- If this interaction test is significant, then the treatment effect can be concluded to differ across subgroups.

Discussion Item #4: Subgroup Analyses

- Post-hoc subgroup analyses are exploratory.
- However, we do not want to ignore a potentially important interaction.
- Observed clinical differences in results across subgroups could be important for device labeling or for further study.

Statistical Summary

- The sponsor appears to have met the primary endpoints of effectiveness and safety.
- The sponsor planned and followed a group sequential design for primary effectiveness, stopping the trial early for superiority.
- Various definitions of withdrawal, crossover, and other deviations make it difficult to assess whether these deviations had an effect on primary endpoint results (or the interim result).

Statistical Summary – continued

- With an unblinded trial, there is a potential for patient as well as physician bias.
- Post-hoc subgroup analyses can help to indicate whether the effectiveness of the device should be studied further within a subgroup.



Expanded Indications for Boston Scientific's CRT-D Devices Based on MADIT-CRT Study FDA Review of P010012 / S230 Post-Approval Study Considerations

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March 18, 2010

Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable

Outline

- General Principles and Objectives for Post-Approval Studies
- Overview and Assessment of Sponsor's Post-Approval Study Outline
- Post-Approval Study Issues for Panel Discussion

General Principles for Post-Approval Studies

- To evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable assurance of device safety and effectiveness
- Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of reasonable assurance of device safety and effectiveness

Objectives of Post-Approval Studies

- Gather postmarket information
 - Long-term performance including effects of re-treatments & device changes
 - Real-world device performance (patients and clinicians)
 - Effectiveness of training programs
 - Sub-group performance
 - Outcomes of concern (safety and effectiveness)
- Account for panel recommendations

Overview of Sponsor's Proposal

Study Design	A single-arm observational study to assess long-term effectiveness by following IDE patients in MADIT-CRT trial for additional three years. No hypothesis and comparison group
Endpoints	1) all cause mortality. 2) all cause mortality or HF events (HF hospitalization or outpatient treatment with IV diuretics), recurrent of HF events, worsening NYHA functional class > II, 6-minute walk test
Population	All active US patients implanted with a CRT-D in MADIT-CRT trial with a maximum of 585 patients
Follow-up	Every 6-month visits, followed through five years (mean follow-up of 2.2 years as of 2/1/2010)
Analysis	Long-term effectiveness in patient subsets

Assessment of Sponsor's Proposal

Study Design: Comparison Group

- Proposal did not include the study hypothesis and comparison group
- Without a comparison group and study hypothesis, it will be difficult to determine whether CRT-D truly provides a long-term beneficial effect

Assessment of Sponsor's Proposal

Study Design: Endpoint

- The primary study objective is to assess long-term effectiveness without a safety evaluation. The premarket MADIT-CRT trial demonstrated that CRT-D implant was associated with increased incidence of adverse events
- Without safety data, it will be difficult to evaluate the long-term risk benefit ratio in CRT-D implant patients, which is a key issue of this PAS

Assessment of Sponsor's Proposal

Study Design: Patient Population

- The patient population of this PAS is all active US patients implanted with CRT-D in the premarket MADIT-CRT trial
- The results from only IDE patients might not represent a true profile of safety and effectiveness of this device in real world patient population

Assessment of Sponsor's Proposal

Analysis of Subsets

- The sponsor proposes to assess the long-term benefits of CRT-D in patient subsets (sex, baseline NYHA class I patients)
- Due to small proportion of patient subsets in the IDE patient population, the proposed PAS will not have enough power to assess the difference in long-term treatment effect in patient subgroups

Issues for Panel Discussion

- Whether are hypothesis tests with a comparison group necessary? and if so, what would be an appropriate comparison group for this study?
- What would be appropriate endpoints for assessment of longer term outcome?
- Whether are subgroup analyses needed and which subgroups should be examined?
- Who would be an appropriate patient population for PAS study and whether new patients should be enrolled?

FDA's Summary

Summary of FDA's Review

- Study fulfilled the predefined primary endpoints
- Limited proportion of NYHA Class I patients
- Increased risks related to LV lead
- Affects of unblinded study design
- Factors likely to influence benefits (LBBB & QRS)

Questions?

Question #1: Evaluation of Safety Background Part 1

- CRT-D therapy was shown to substantially increase the risk of system-related complications. There was a 7.5% absolute and 97% relative increase in system-related complications within the first 91 days (84.8% system-related complication-free rate with CRT-D therapy as compared to a rate of 92.3% with ICD therapy). The left ventricular lead accounts for the difference, with 8% of the patients experiencing complications directly related to the left ventricular lead. In addition to left ventricular lead-related complications, there were more pneumothoraces and device pocket erosions in the CRT-D group.

Question #1: Evaluation of Safety Background Part 2

- Overall, the proportion of patients experiencing complications from any cause at any time is similar (60.4% of the patients in the CRT-D group and 59.7% of the patients in the ICD group). The number of complications per device-month is also similar. Therefore, it appears that the reduction in complications related to heart failure hospitalizations in the CRT-D group is accompanied by an increase in system-related complications related to the CRT-D system and left ventricular lead. The following tables summarize the results.

Question #1: Evaluation of Safety

Background Part 3

Summary of All Complications

Adverse Event	% of Patients	
	CRT-D	ICD
Subtotal PG Related Events	5.9%	4.4%
Subtotal RA Lead Related Events	4.3%	1.7%
Subtotal RV Lead Related Events	1.9%	2.1%
Subtotal LV Lead Related Events	8.0%	0.8%
Subtotal Defibrillator Lead Related Events	0.5%	0.7%
Subtotal Procedure Related Events	7.9%	5.5%
Subtotal Protocol Testing Related Events	0.1%	0%
Subtotal Cardiovascular - HF Related Events (worsening heart failure)	15.7%	25.9%
Subtotal Cardiovascular - Non-HF Related Events	27.5%	28.9%
Subtotal Non-cardiovascular Related Events	34.0%	35.0%
Total Adverse Events	60.4%	59.7%

Question #1: Evaluation of Safety

Background Part 4

System-Related Complications

Complication	% of Patients	
	CRT-D	ICD
LV Lead	5.2%	-
RA Lead	3.2%	1.4%
RV Lead	1.4%	1.8%
PG	1.5%	1.1%
Procedure	6.9%	3.8%
Other	0.2%	0.3%
Total System-Related Complications	15.1%	7.5%

Question #1: Evaluation of Safety

QUESTION: Please comment on the increase in system-related complications related to the CRT-D system and left ventricular lead. How significant is this increase in complication rate compared to the reduction in heart failure hospitalizations noted in the CRT-D group?

Question #2: Effectiveness Data Background Part 1

- The primary effectiveness endpoint includes both all-cause mortality and heart failure events. CRT-D therapy was associated with a 34% reduction in the relative risk of death or heart failure event as compared to ICD therapy. Overall, 21% of the total patients had primary endpoint events during the study (17% in the CRT-D group and 26% in the ICD group). Of the patients with primary endpoint events, 86% of the heart failure events were inpatient heart failure hospitalizations (90% in the CRT-D group and 76% in the ICD group). The proportion of patients with all-cause mortality at any time was 7% (7% in the CRT-D group and 7% in the ICD group). As a result, there was no difference in the all-cause mortality rates with a hazard ratio of 1.01 ($p=0.970$). It is also important to note that outpatient heart failure events only accounted for a small proportion, 11% overall, of the total primary endpoint events that occurred during the study. The following table and figure summarize the results.

Question #2: Effectiveness Data Background Part 2

Primary Effectiveness Endpoint Components

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

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

Question #2: Effectiveness Data

QUESTION: The primary effectiveness outcome for CRT-D was driven primarily by a reduction in the inpatient heart failure hospitalization rates without a reduction in mortality and no improvement was noted in functional assessment compared to the ICD group. Please comment on the significance of the effectiveness results. In addressing this question please include what effect, if any, the lack of patient and physician blinding may have had on determination of CRT-D effectiveness.

Question #3: Patient Composition Background

- Although the study allowed the enrollment of patients with NYHA Class I and II, only ~15% of the patients were NYHA Class I. In addition, it appears that patients enrolled in the trial are not as healthy as typical NYHA Class I-II patients. Approximately 40% of the patients were previously hospitalized for heart failure, and 10% of the patients were previously NYHA Class III-IV greater than 3 months prior to enrollment. The 6MWT distances also seem more consistent with a NYHA Class II-III population. These examples indicate that the patients enrolled in the MADIT-CRT study might not fully represent the typical NYHA Class I / II patients with reduced LVEF. In addition, although over 90% of the patients were prescribed beta blockers, only ~25% of the patients had achieved a target dosage of beta blockers at enrollment.

Question #3: Patient Composition

- QUESTION 3A: For what population of patients in a community setting are results of the MADIT-CRT trial generally applicable? Please specifically address whether the limited enrollment of NYHA Class I patients warrant indicating CRT D therapy in this population?
- QUESTION 3B: Are there other specific subpopulations where CRT-D therapy should not be indicated (e.g., NYHA Class I, QRS duration < 150 ms, non-LBBB [Left Bundle Branch Block])?

Question #4: Indications for Use Background

The company has proposed the following Indications for Use:

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

- Moderate to severe heart failure (NYHA Class III-IV) with EF < 35% and QRS duration > 120 ms
- Mild heart failure (NYHA Class II) with EF < 30% and QRS duration > 130 ms
- Asymptomatic heart failure (NYHA Class I) of ischemic origin with EF < 30% and QRS duration > 130 ms"

Question #4: Indications for Use

- QUESTION: Do the proposed indications appropriately define those patients that are likely to benefit from CRT-D based on the results of the MADIT-CRT study?
- QUESTION: If the answer to the previous question is "no", what changes should be made to the proposed wording? Would further clarifications of the patient characteristics or the requirements for stable and optimal pharmacologic therapy be appropriate? Are there other recommended changes to the labeling?

Question #5: Post-Approval Study Background

- There are currently 585 active U.S. patients that have been implanted with the sponsor's CRT-D system as part of the MADIT-CRT study. The sponsor has proposed to approach all of these patients to request their participation in a post-approval study. No new patients would be implanted. These existing patients would be followed for a total of 5 years.

Question #5: Post-Approval Study

- QUESTION: Is a post-approval study necessary to further evaluate the risks and benefits associated with CRT-D therapy in the intended patient population, especially in patients with NYHA Class I functional status? If the answer is yes, please comment on general study design parameters that would be important to incorporate in such a study.