

# **Medtronic Cardiac Resynchronization Therapy with Implantable Cardioverter Defibrillator (CRT-D) for Mildly Symptomatic Heart Failure**

**FDA Circulatory Systems Panel  
December 7, 2011  
Sponsor Presentation**

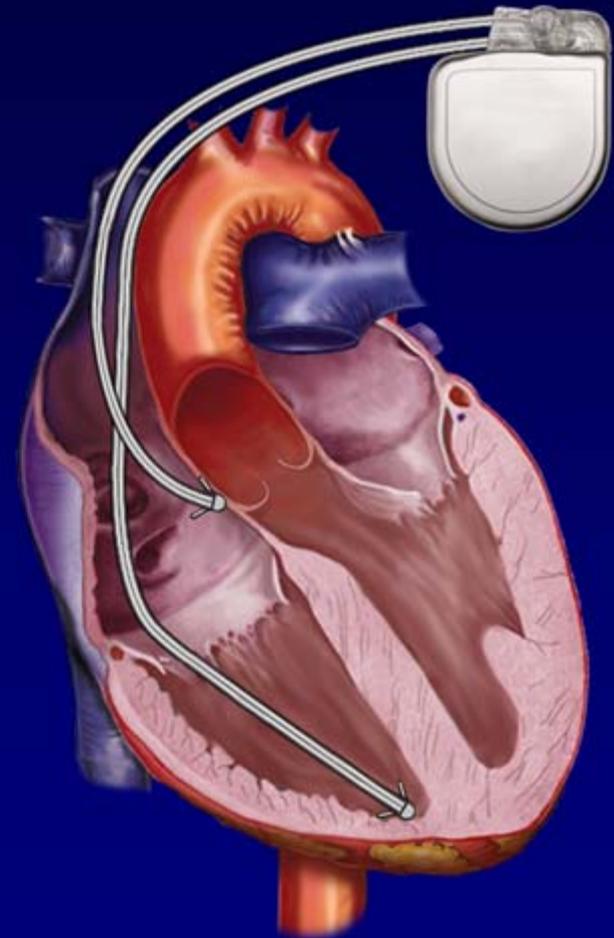
# **Introduction**

**Marshall Stanton, MD**

**Vice President, Clinical Research  
Medtronic Cardiac and Vascular Group**

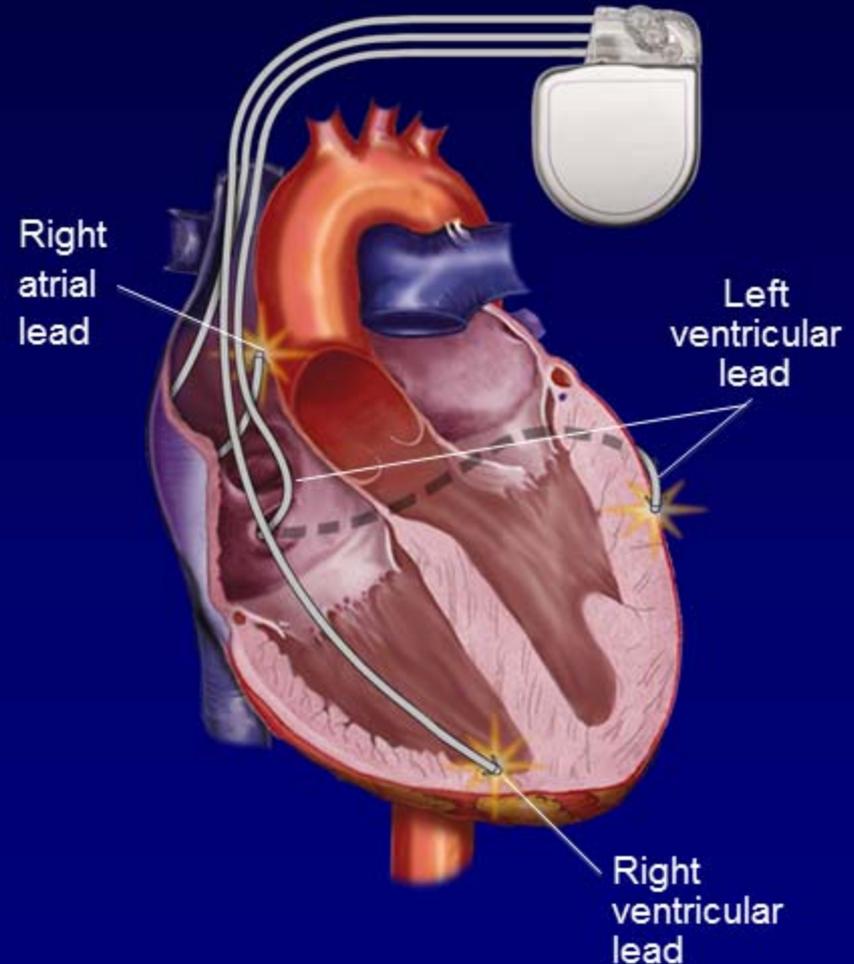
# Dual-Chamber ICD System

- Provides pacing with defibrillation capabilities
- Composed of:
  - Pulse generator
  - Right atrial pacing and sensing lead
  - Right ventricular pacing plus defibrillation lead



# CRT-D System Adds LV Lead to an ICD System

- Provides Biventricular Pacing With ICD Capability
- Composed of:
  - Pulse generator
  - Right atrial pacing and sensing lead
  - Right ventricular pacing plus defibrillation lead
  - Left ventricular pacing lead
- Implant of right atrial and right ventricular leads is the same as a dual chamber ICD



# CRT proven to reverse HF progression in NYHA Class III/IV

	Mortality	HF or CV Hospitalizations	Cardiac Function/ Structure	Quality of Life	Exercise Capacity	NYHA Class
CARE-HF <sup>1,2</sup>	+	+	+	Reported improvement, but not blinded		
COMPANION <sup>3</sup>	+	+	Not collected			
MIRACLE <sup>4</sup>	Not powered for mortality or hospitalization		+	+	+	+
MIRACLE ICD <sup>5</sup>			+	+	-	+

<sup>1</sup> *N Engl J Med.* 2005;352(15):1539-1549.

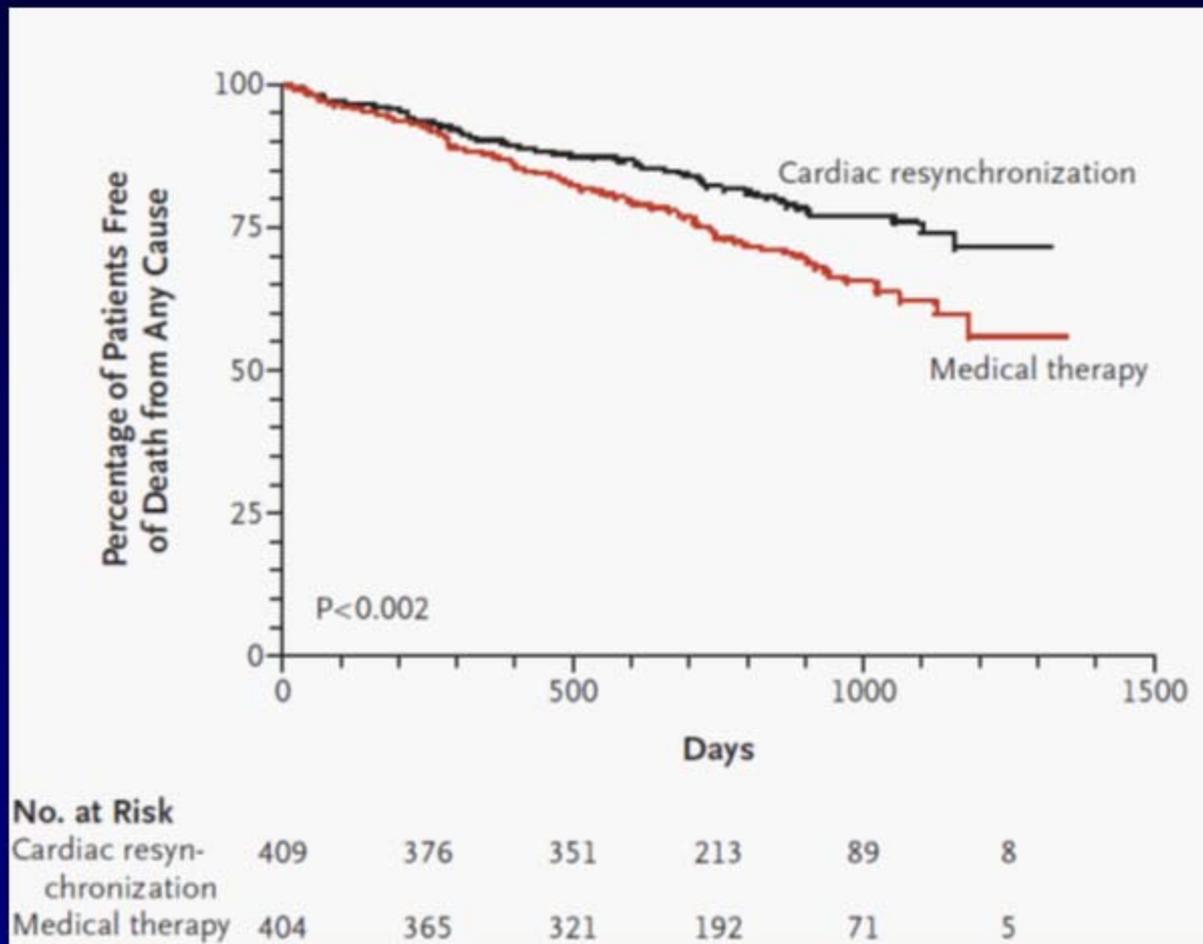
<sup>2</sup> *Eur Heart J.* 2006;27(16):1928-1932.

<sup>3</sup> *J Card Fail.* 2000;6(3):276-285.

<sup>4</sup> *N Engl J Med.* 2002;346(24):1845-1853.

<sup>5</sup> *JAMA.* 2003;289(20):2685-2694.

# Survival Curve from CARE-HF



Cleland JGF et al. The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure, N Eng J Med 2005;352:1539-49.

# Studies Supporting CRT-D Expansion

	REVERSE	RAFT
<b>Study design</b>	Randomized 2:1 CRT±D ON vs OFF Double-blinded	Randomized 1:1 CRT-D vs ICD Double-blinded
<b>Size</b>	610 randomized	1798 randomized
<b>Randomized Duration</b>	12 months (U.S., Canada) 24 months (Europe)	18 months minimum; Mean 40 months
<b>Primary endpoint</b>	HF Clinical Composite	Total mortality + HF hospitalization
<b>NYHA Class</b>	I and II	II and III

# Proposed Patient Population

- **CRT-D  
(ICD-indicated)**
- **NYHA Class II**
- **LVEF  $\leq$  30%**
- **QRS  $\geq$  120 ms**
- **Left Bundle  
Branch Block**

# Agenda

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Introduction

**Marshall Stanton, MD**

VP, Clinical Research  
Medtronic Cardiac and Vascular Group

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REVERSE Study Design  
And Results

**Michael R. Gold, MD, PhD**

Michael E. Assay Prof. of Medicine  
Director of Cardiology  
Medical University of South Carolina  
REVERSE Steering Committee  
REVERSE Adverse Event Advisory Committee

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RAFT Study Design  
and Results

**Anthony Tang, MD**

University of British Columbia  
RAFT Principal Investigator  
RAFT Executive Committee Chair

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Totality of Evidence from  
REVERSE and RAFT

**William T. Abraham, MD, FACP, FACC, FAHA**

Prof. of Medicine, Physiology, and Cell Biology  
Chair of Excellence in Cardiovascular Medicine  
The Ohio State University  
REVERSE Steering Committee

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Perspective on FDA  
Questions and Conclusions

**Marshall Stanton, MD**

VP, Clinical Research  
Medtronic Cardiac and Vascular Group

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# Additional Experts

## George Wells, PhD

Director, Cardiac Methods Research Centre  
Prof., Dept. of Epidemiology and Community Medicine  
University of Ottawa Heart Institute  
RAFT Methodologist and Biostatistician

## Jeff Cerkvenik, MS

Senior Principal Statistician  
Medtronic, Inc.

**REVERSE: REsynchronization  
reVErseS Remodeling in Systolic left  
vEntricular dysfunction**

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

**Michael R. Gold, MD, PhD**  
*Medical University of South Carolina*  
**REVERSE Steering Committee**  
**REVERSE Adverse Event Advisory  
Committee**

# REVERSE Agenda

- **Study Design**
- **Overall Results**
- **Safety**
- **Subgroup Results**

## **REVERSE: Purpose**

- **To determine the effects of CRT with or without an ICD on disease progression:**
  - **NYHA Class I or II HF / reduced EF / prolonged QRS**

# REVERSE: Study Design

- **Prospective, randomized, double-blind, multicenter**
  - **73 international centers**
    - 37 U.S., 35 Europe, 1 Canada
  - **683 planned enrollment**
  - **Randomized 2:1 (CRT ON : CRT OFF)**
- **Enrollment**
  - **September 2004 through September 2006**
- **Follow-up**
  - **40 ± 5 months**

# **REVERSE: Study Oversight**

- **Steering Committee**
- **Data Monitoring Committee**
- **Adverse Event Advisory Committee**
- **Echo Core Laboratories**

# REVERSE: Key Inclusion/Exclusion Criteria

## Inclusion

- NYHA Class II or I (ACC/AHA Stage C)
- QRS  $\geq$  120 ms
- LVEF  $\leq$  40%; LVEDD  $\geq$  55 mm
- Optimal medical therapy
- Without permanent cardiac pacing
- With or without an ICD indication

## Exclusion

- NYHA Class III or IV within 90 days prior to enrollment
- HF hospitalization within 90 days prior to enrollment
- Acute coronary syndrome, acute MI, CABG, or PCI within 90 days prior
- Persistent or permanent atrial arrhythmias

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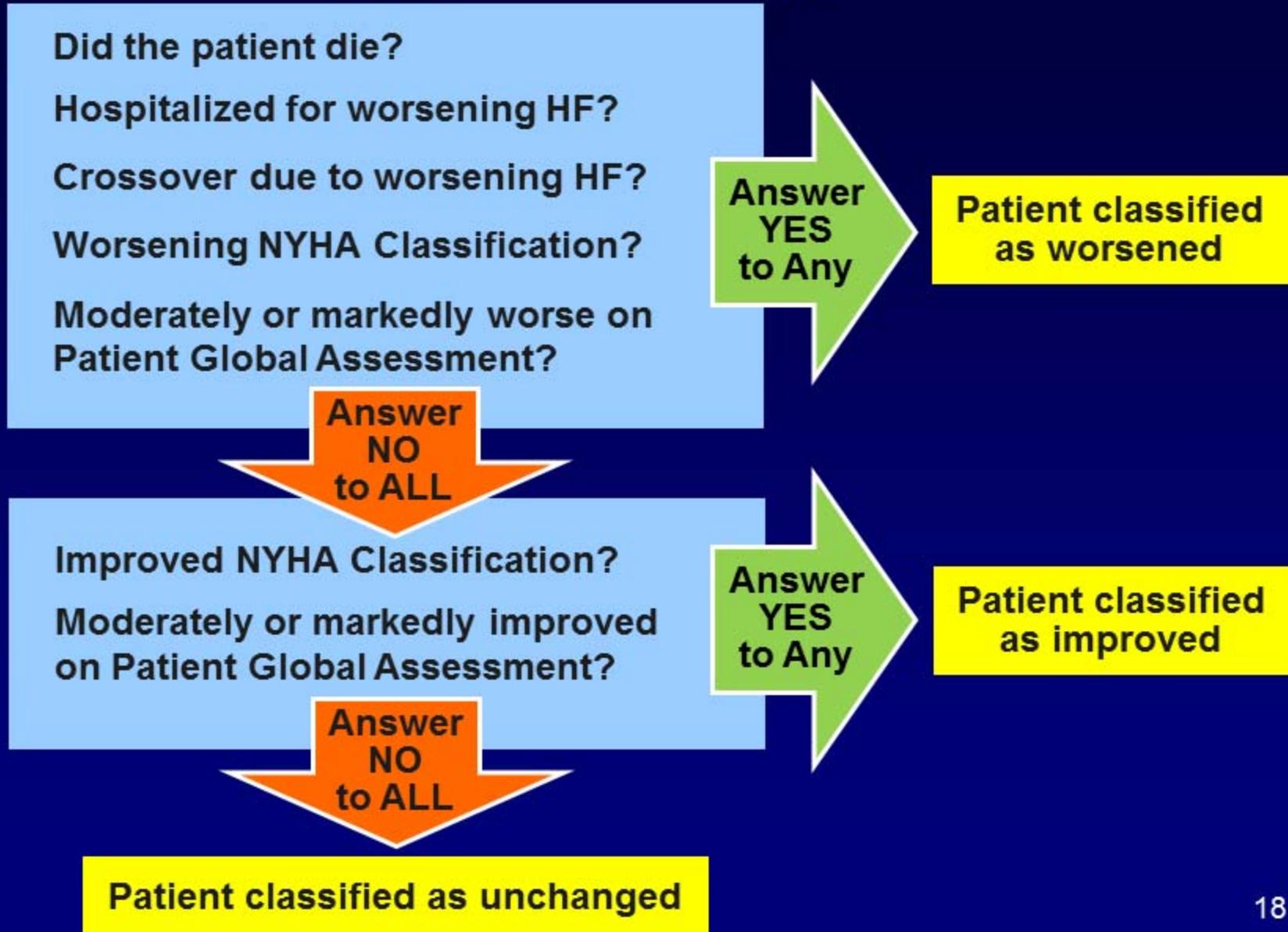
82%  
NYHA Class II

83% received  
CRT-D

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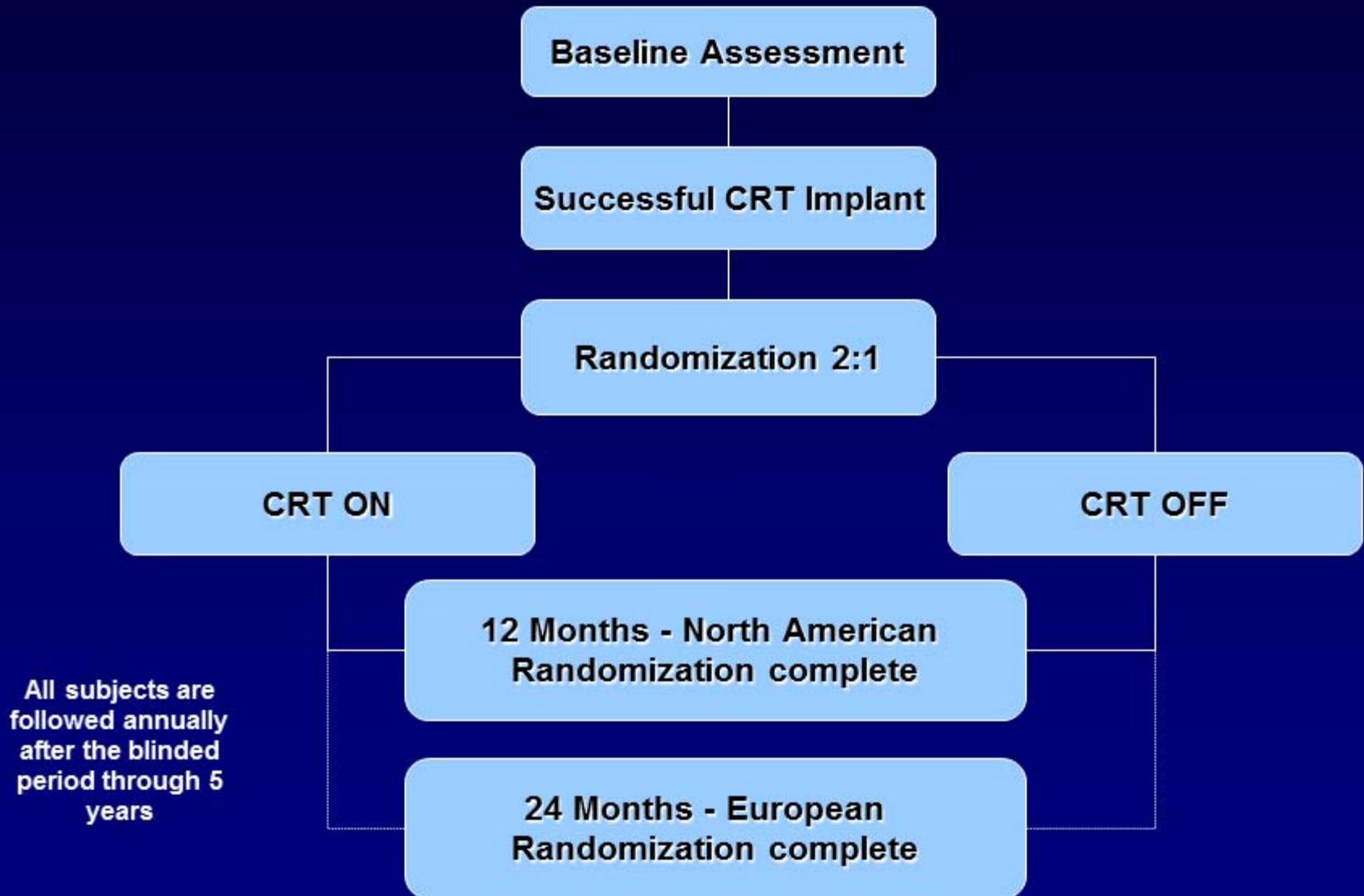
# Clinical Composite Response



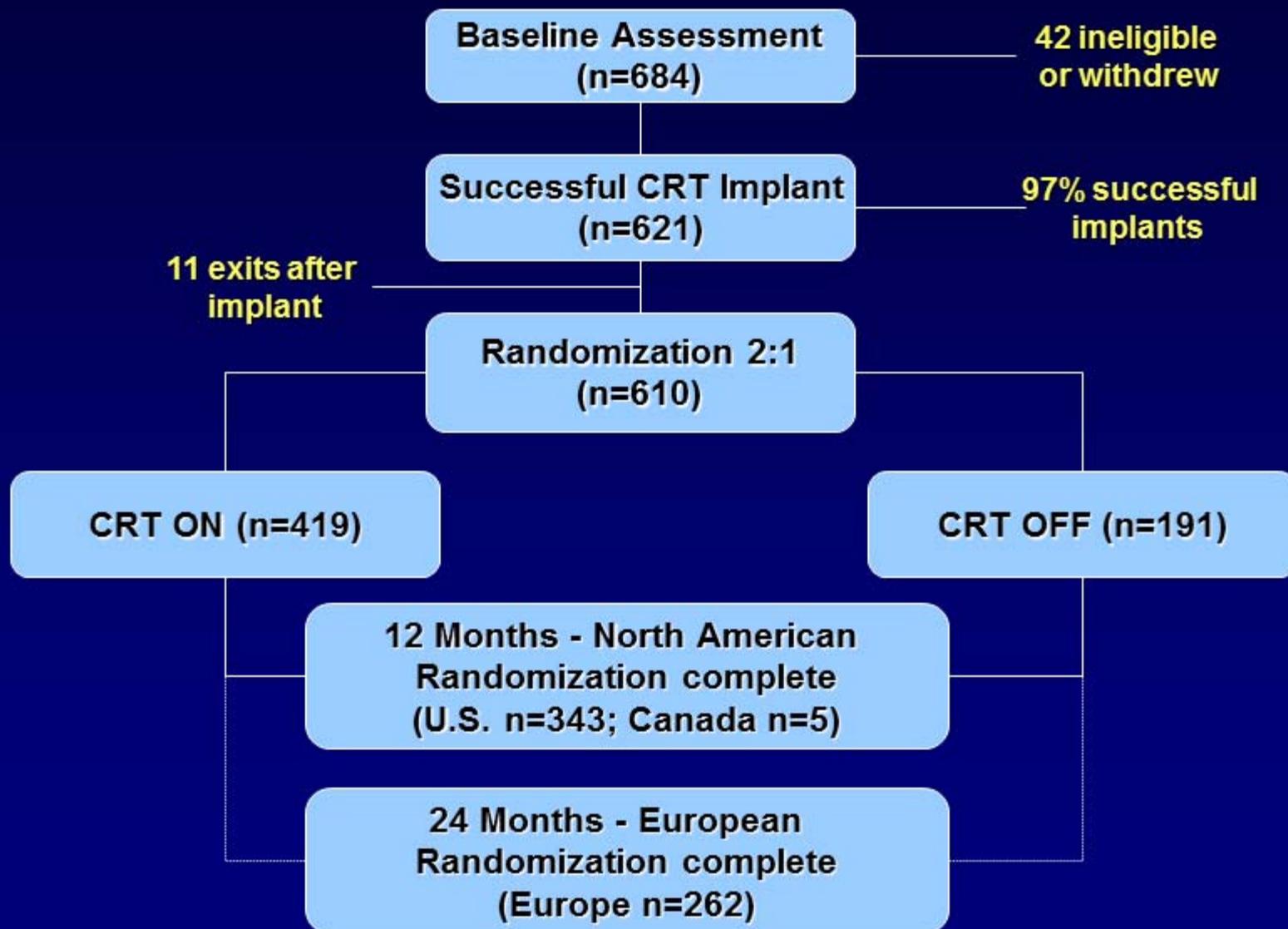
# REVERSE: Statistical Methods

- All analyses are intention-to-treat
- Sample Size Assumptions (based on MIRACLE ICD trial)
  - Primary Endpoint: Clinical Composite Response
    - **CRT ON: 22% worsened, CRT OFF: 34% worsened**
    - Alpha=0.05, Power=80%
    - Attrition of 25% from implant to randomization
    - Calculated enrollment sample size = **683**
  - Secondary Endpoint: LVESVi
    - Change: CRT ON = -14 ml/m<sup>2</sup> ± 31, CRT OFF = -6 ml/m<sup>2</sup> ± 26
    - Alpha=0.05, Power=80%
    - Attrition of 15% post-randomization
    - Calculated enrollment sample size = **644**

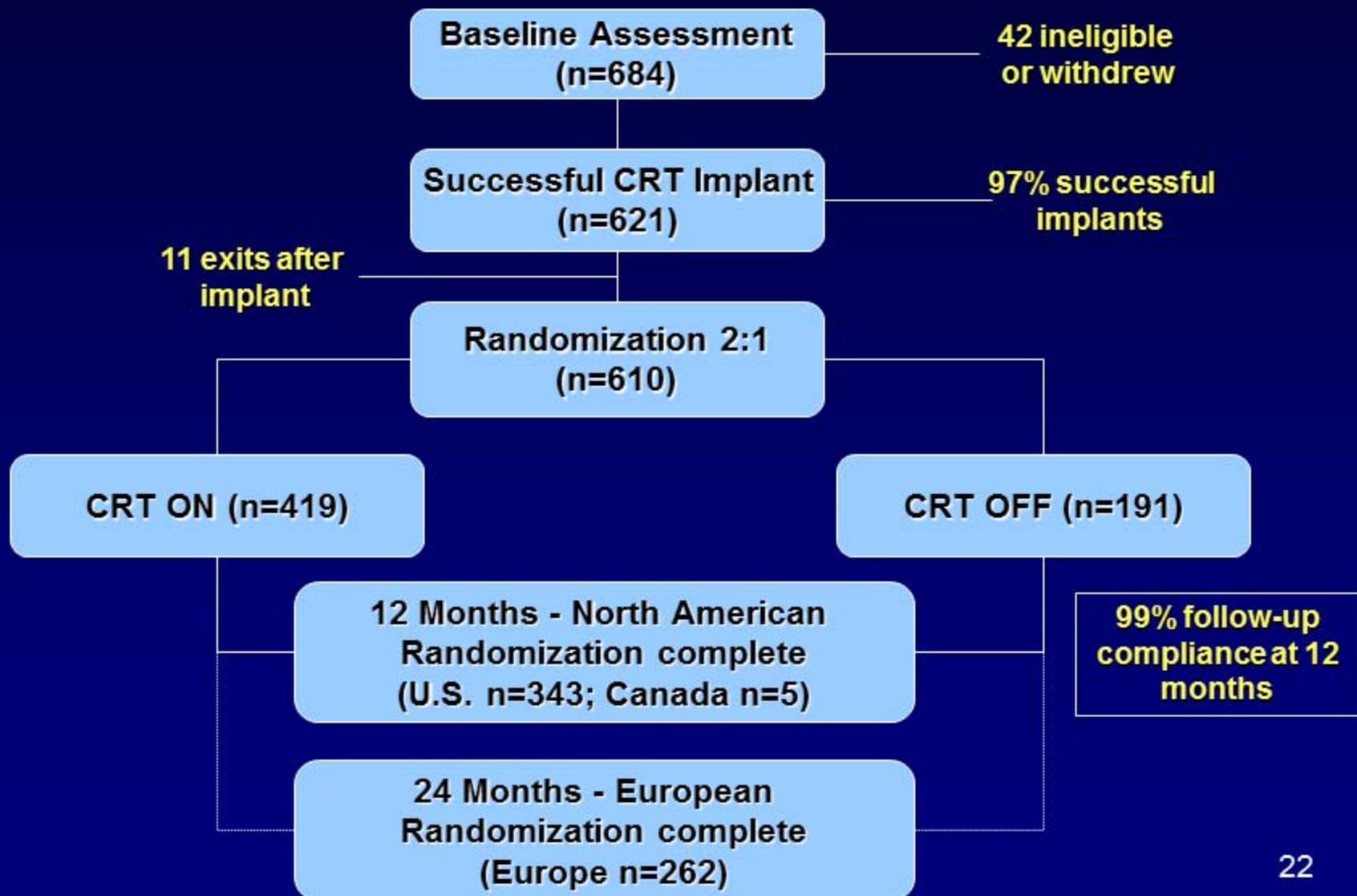
# REVERSE: Study Schematic



# REVERSE: Enrollment and Randomization



# REVERSE: Enrollment and Randomization



## REVERSE: Balanced Distribution of Baseline Characteristics

	CRT OFF n=191	CRT ON n=419	P-value
<b>Age (yrs)</b>	61.8 ± 11.6	62.9 ± 10.6	0.26
<b>Male</b>	80%	78%	0.75
<b>NYHA II</b>	83%	82%	0.82
<b>ICD</b>	85%	82%	0.41
<b>LVEF (%)</b>	26.4 ± 7.1	26.8 ± 7.0	0.50
<b>QRS (ms)</b>	154 ± 24	153 ± 21	0.41
<b>LBBB</b>	59%	62%	0.59
<b>Ischemic</b>	51%	56%	0.22
<b>Beta blockers</b>	94%	96%	0.32
<b>ACE-i/ ARB</b>	97%	96%	0.63

# REVERSE: Balanced Distribution of Baseline Characteristics

	CRT OFF n=191	CRT ON n=419	P-value
<b>Age (yrs)</b>	<b>61.8 ± 11.6</b>	<b>62.9 ± 10.6</b>	<b>0.26</b>
<b>Male</b>	<b>80%</b>	<b>78%</b>	<b>0.75</b>
<b>NYHA II</b>	<b>83%</b>	<b>82%</b>	<b>0.82</b>
<b>ICD</b>	<b>85%</b>	<b>82%</b>	<b>0.41</b>
<b>LVEF (%)</b>	<b>26.4 ± 7.1</b>	<b>26.8 ± 7.0</b>	<b>0.50</b>
<b>QRS (ms)</b>	<b>154 ± 24</b>	<b>153 ± 21</b>	<b>0.41</b>
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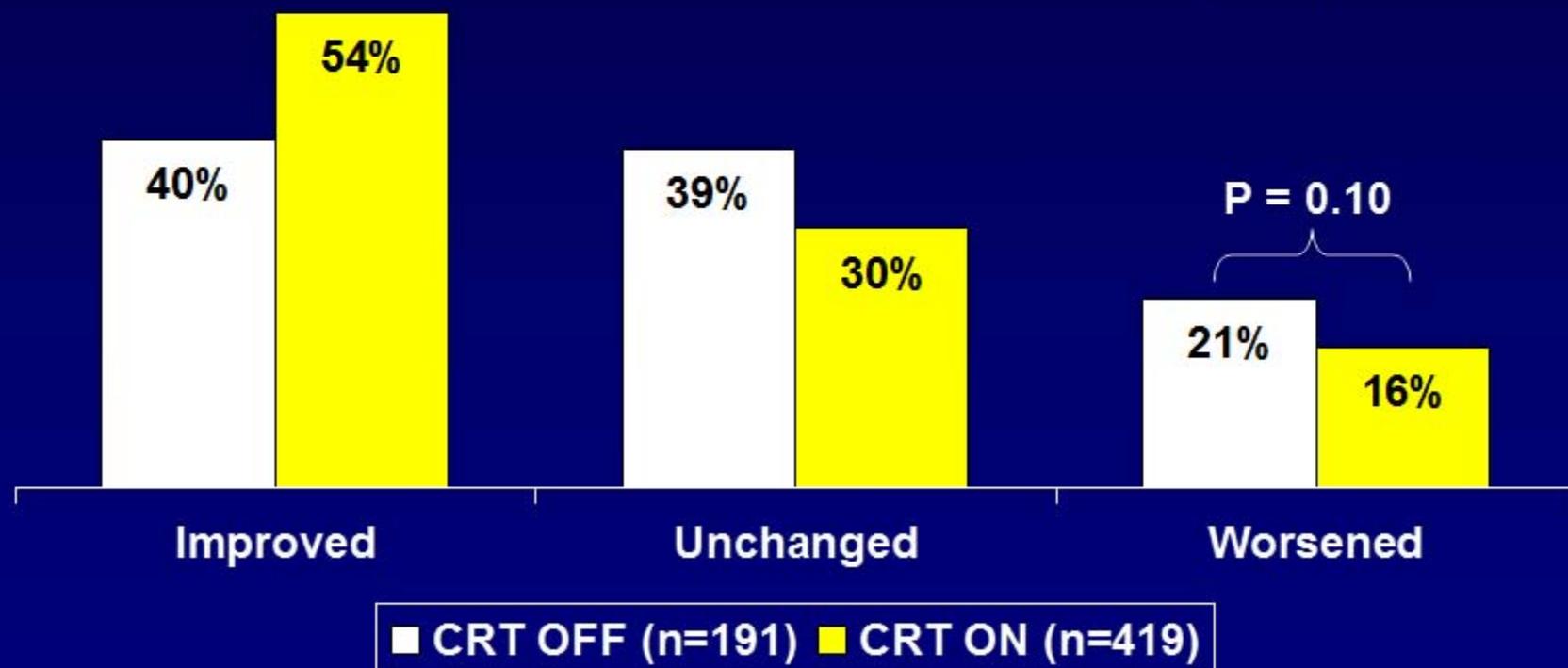
# **REVERSE: Primary Endpoint**

## **Clinical Composite Response**

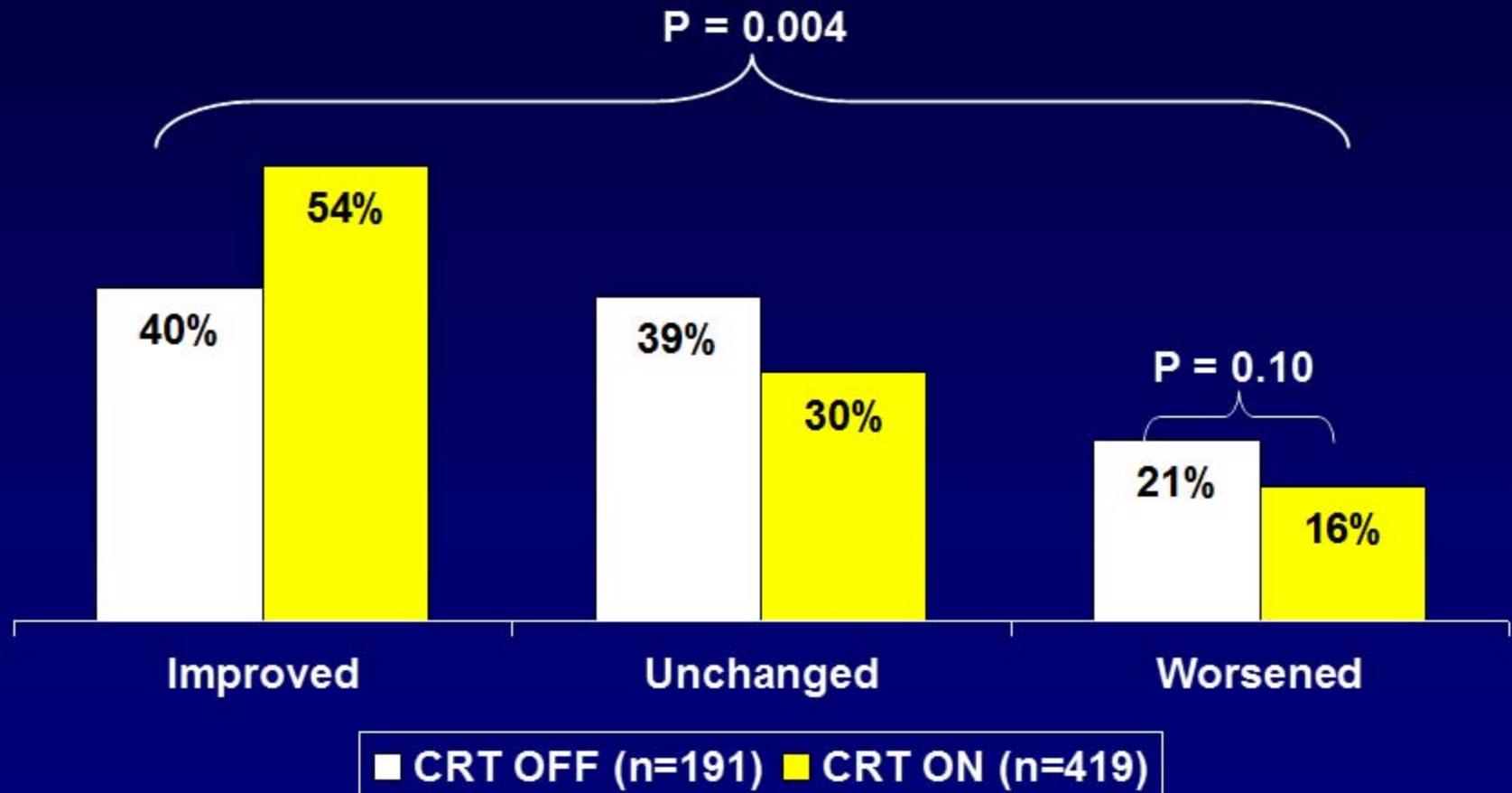
- **Considered Worsened if:**
  - **Death from any cause**
  - **Heart failure hospitalization**
  - **Crossover due to worsening heart failure**
  - **NYHA class worsened**
  - **Patient global assessment worsened**
- **Considered Improved if:**
  - **NYHA class improved**
  - **Patient global assessment improved**

# REVERSE Primary End Point: % Worsened at 12 Months

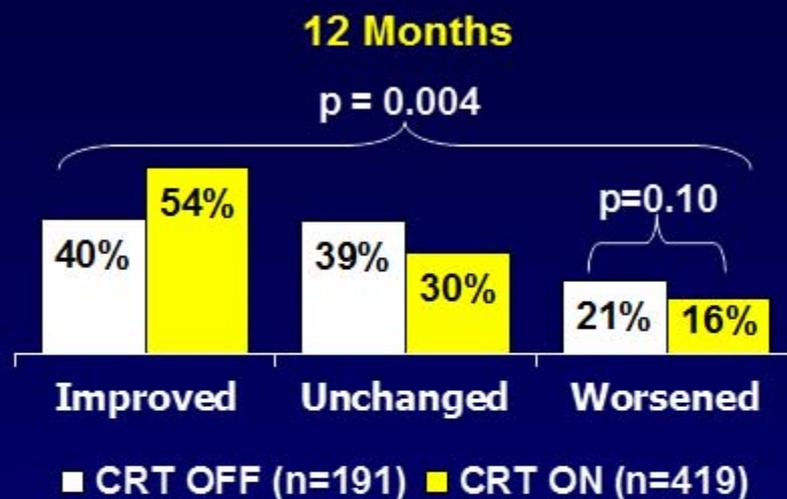
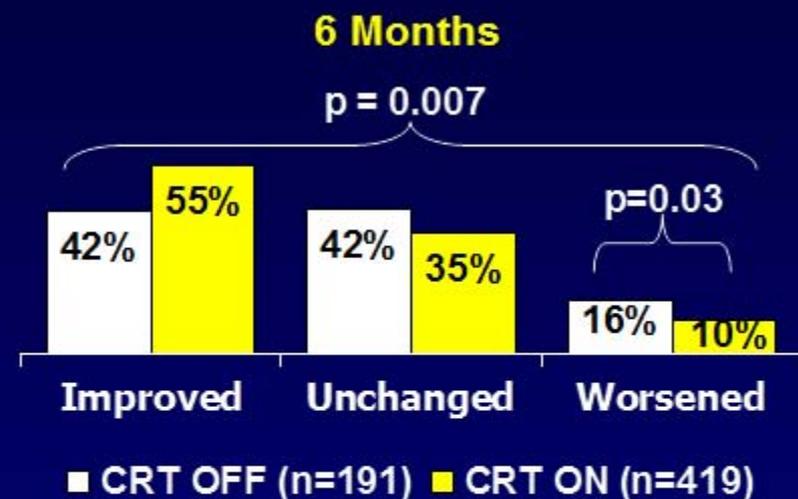
Primary Endpoint Not Met



# REVERSE: Full Distribution at 12 Months

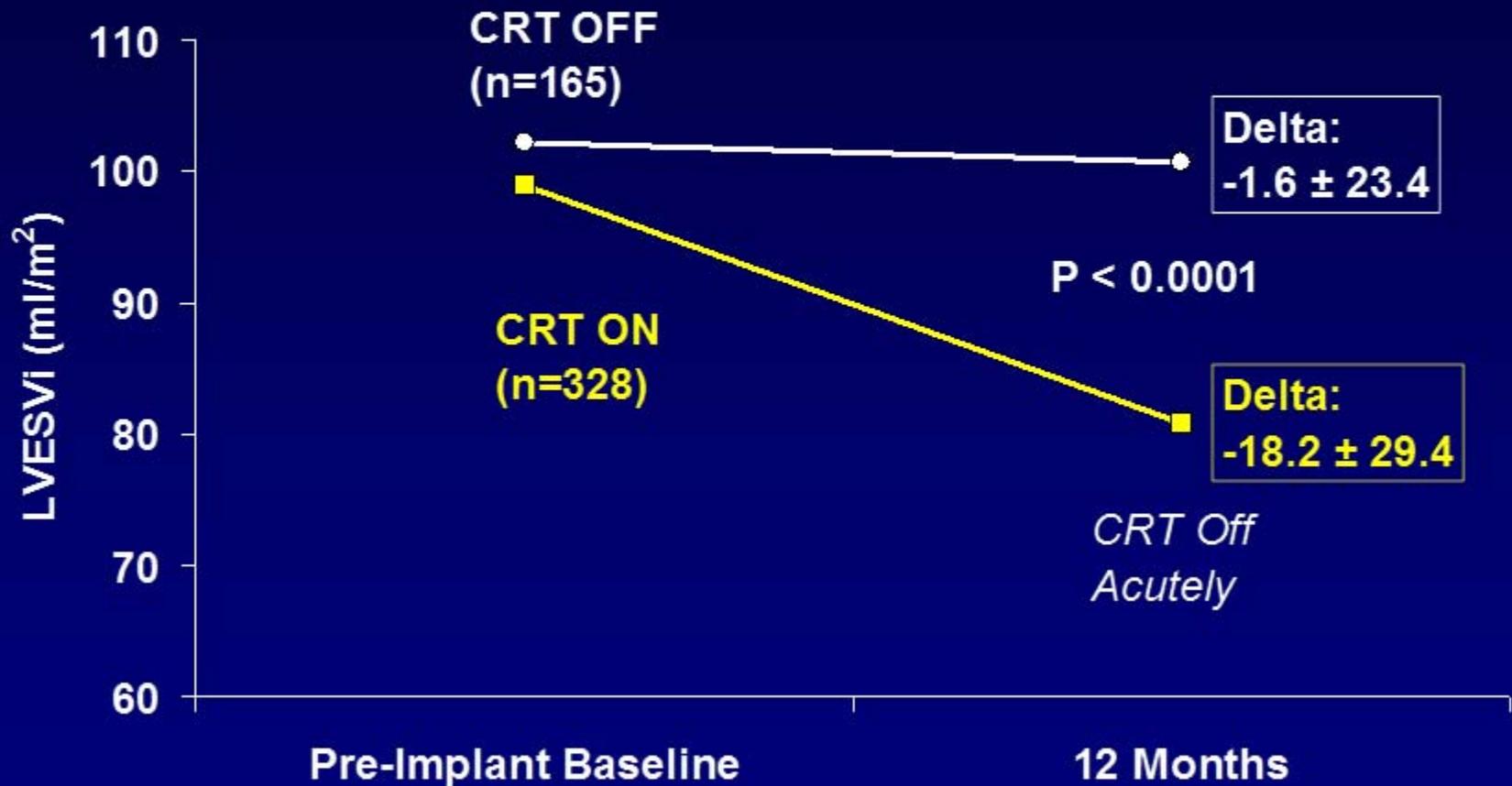


# REVERSE: Consistent Benefit Over Time



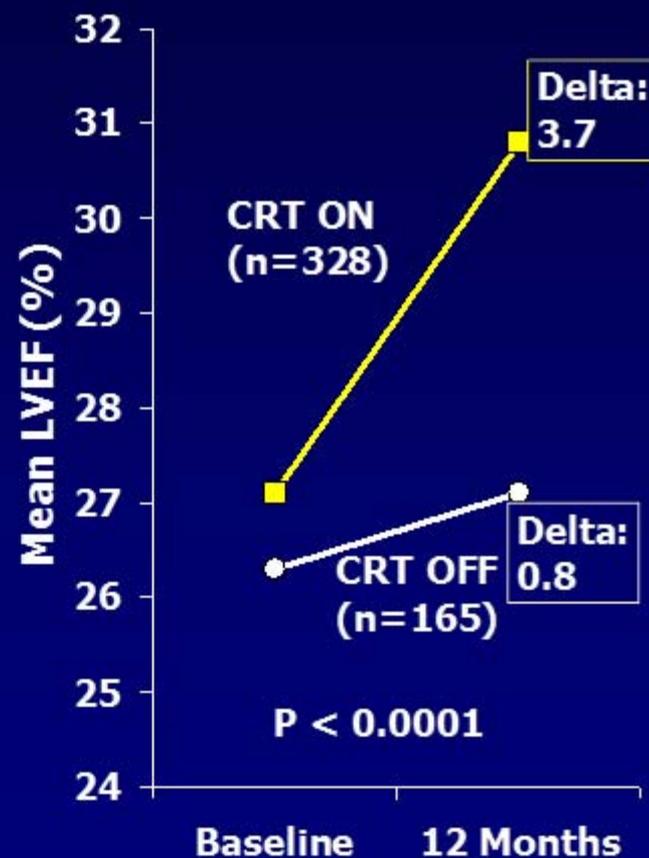
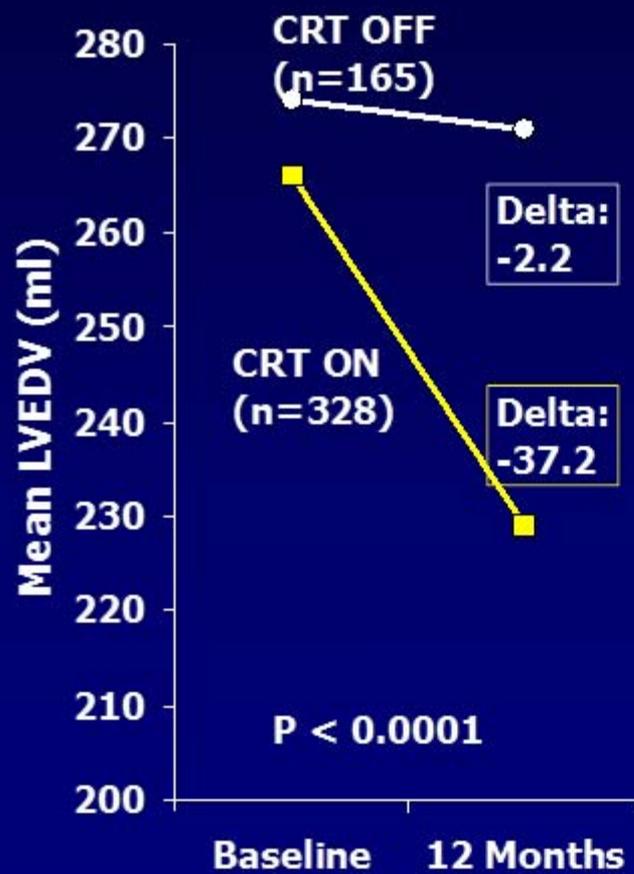
\* Europe only

# REVERSE Secondary Endpoint: Significant Reduction in Left Ventricular End Systolic Volume Index (LVESVi)



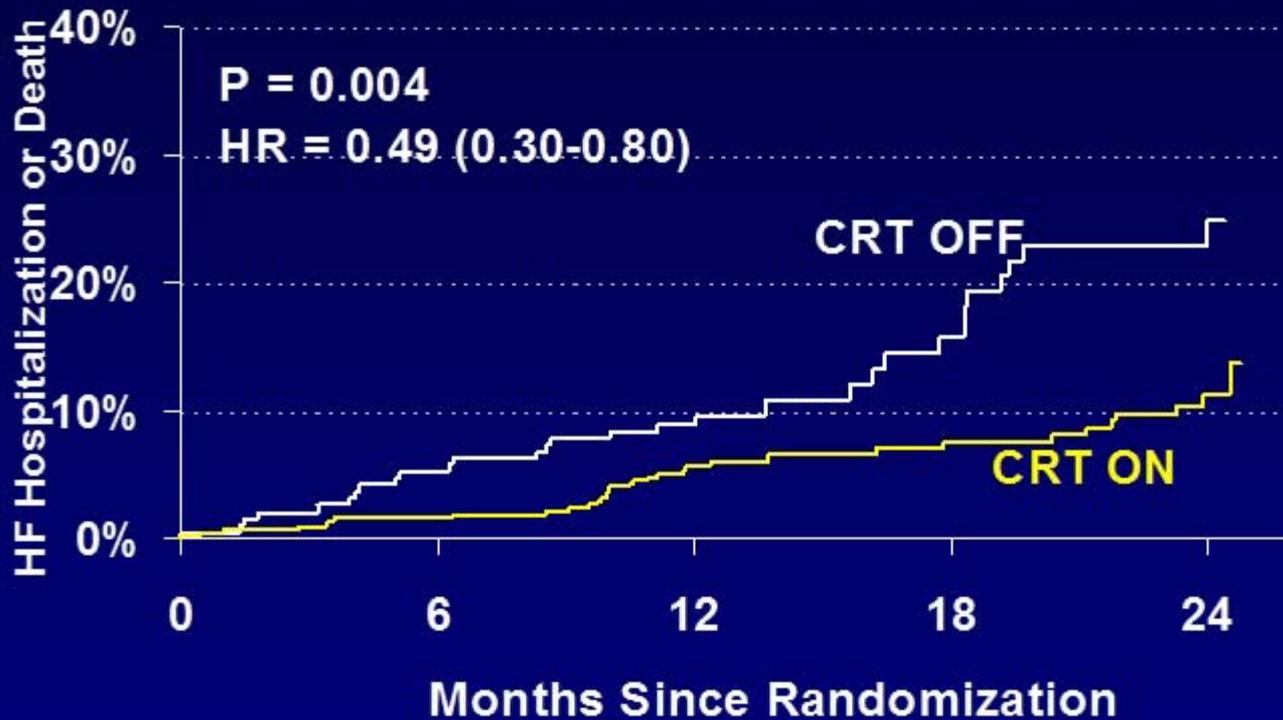
Analysis includes only paired data

# Secondary Endpoint: Echo Measures Indicate Change in Cardiac Structure with CRT



Analysis includes only paired data

# REVERSE: Significant Reduction in HF Hospitalization or All-cause Death



Number	191	181	126	70	39
remaining	419	412	282	169	77

# REVERSE: Mortality



	0	6	12	18	24
Number remaining	191	191	134	78	47
Number remaining	419	414	290	175	83

# REVERSE Adverse Events

- **Adverse Event Committee classified:**
  - **Complication**
    - Invasive intervention, or
    - Termination of significant device function
  - **Observation**
    - NO invasive intervention, or
    - NO termination of significant device function

# REVERSE Safety: Left Ventricular Lead Complication Rate Similar to Previous Trials

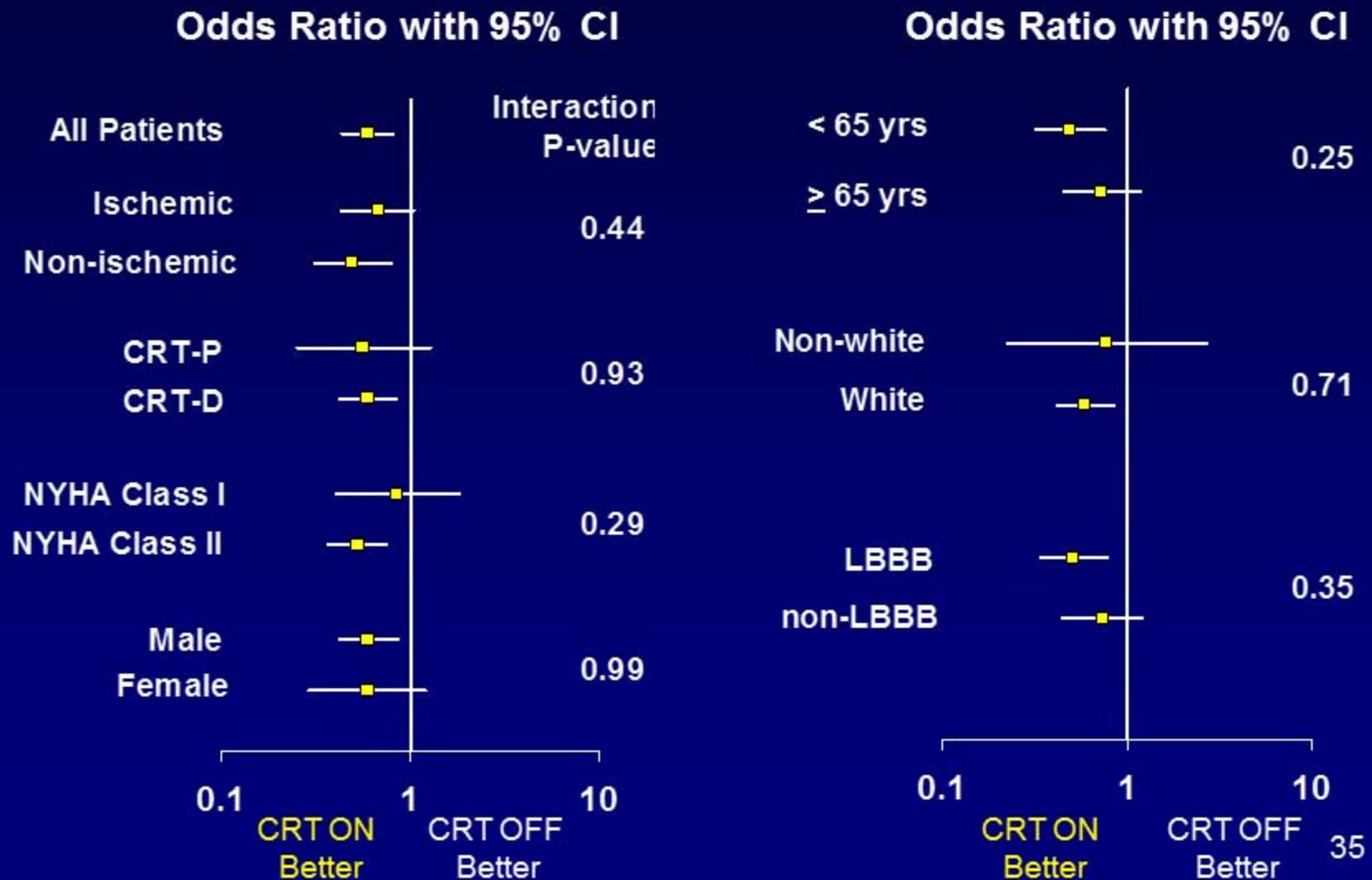


Number  
remaining **621**

**547**

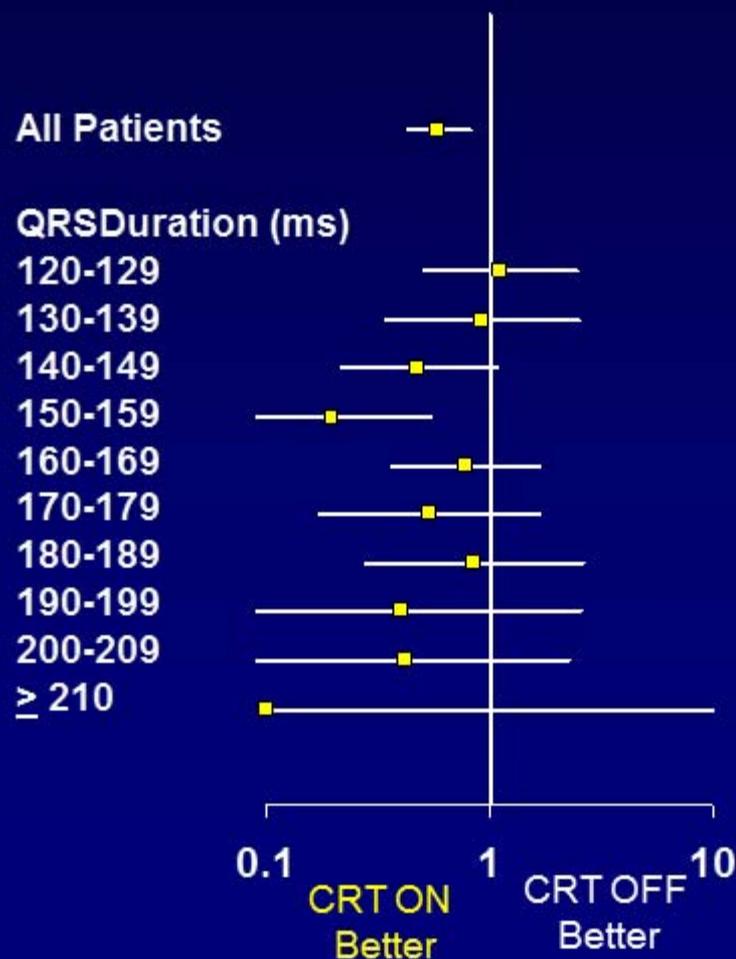
**518**

# REVERSE: CRT Beneficial Across Subgroups in Clinical Composite Response Distribution

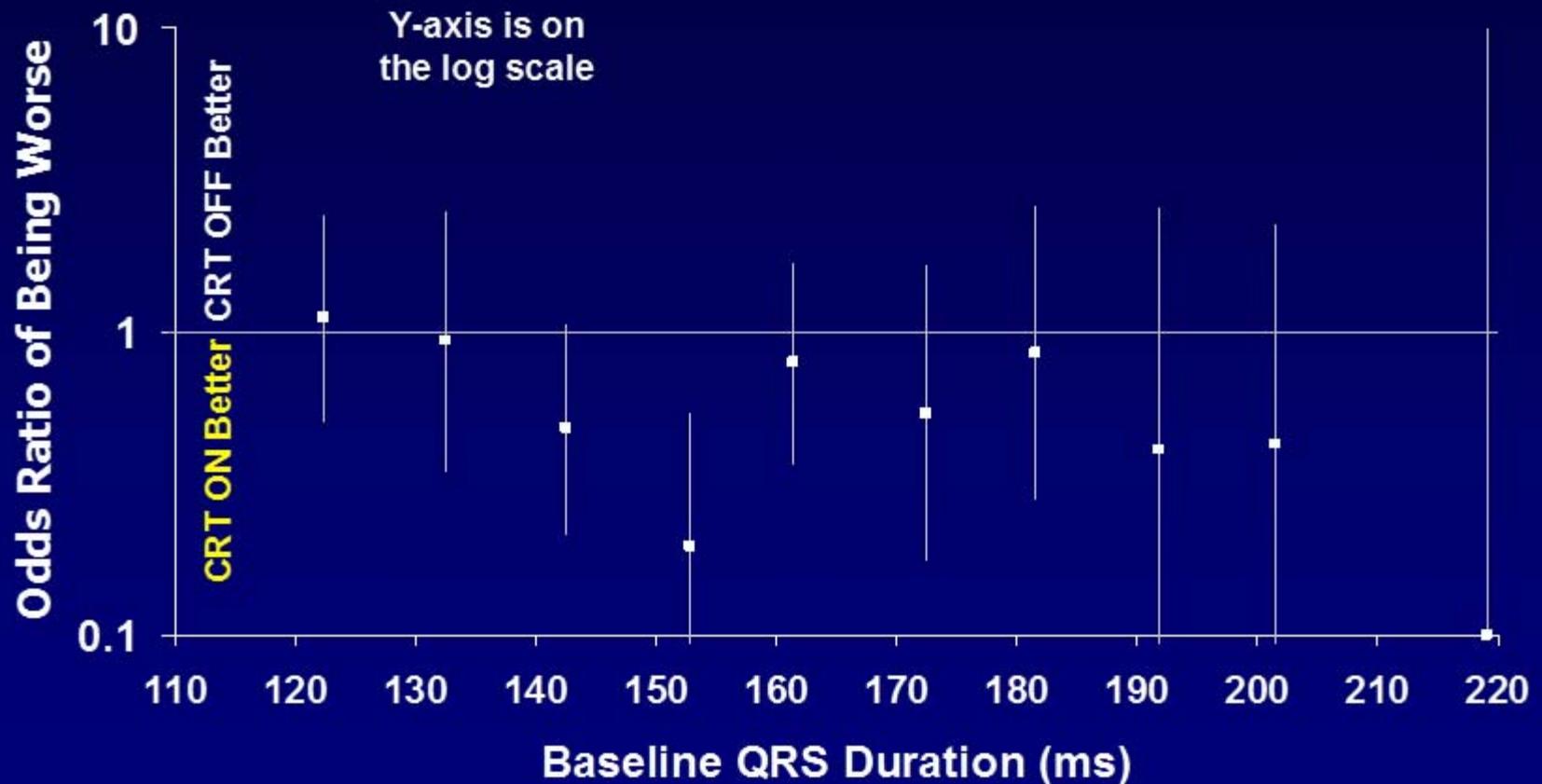


# REVERSE: Clinical Composite Distribution Subgroup Analysis of QRS Duration

Odds Ratio with 95% CI

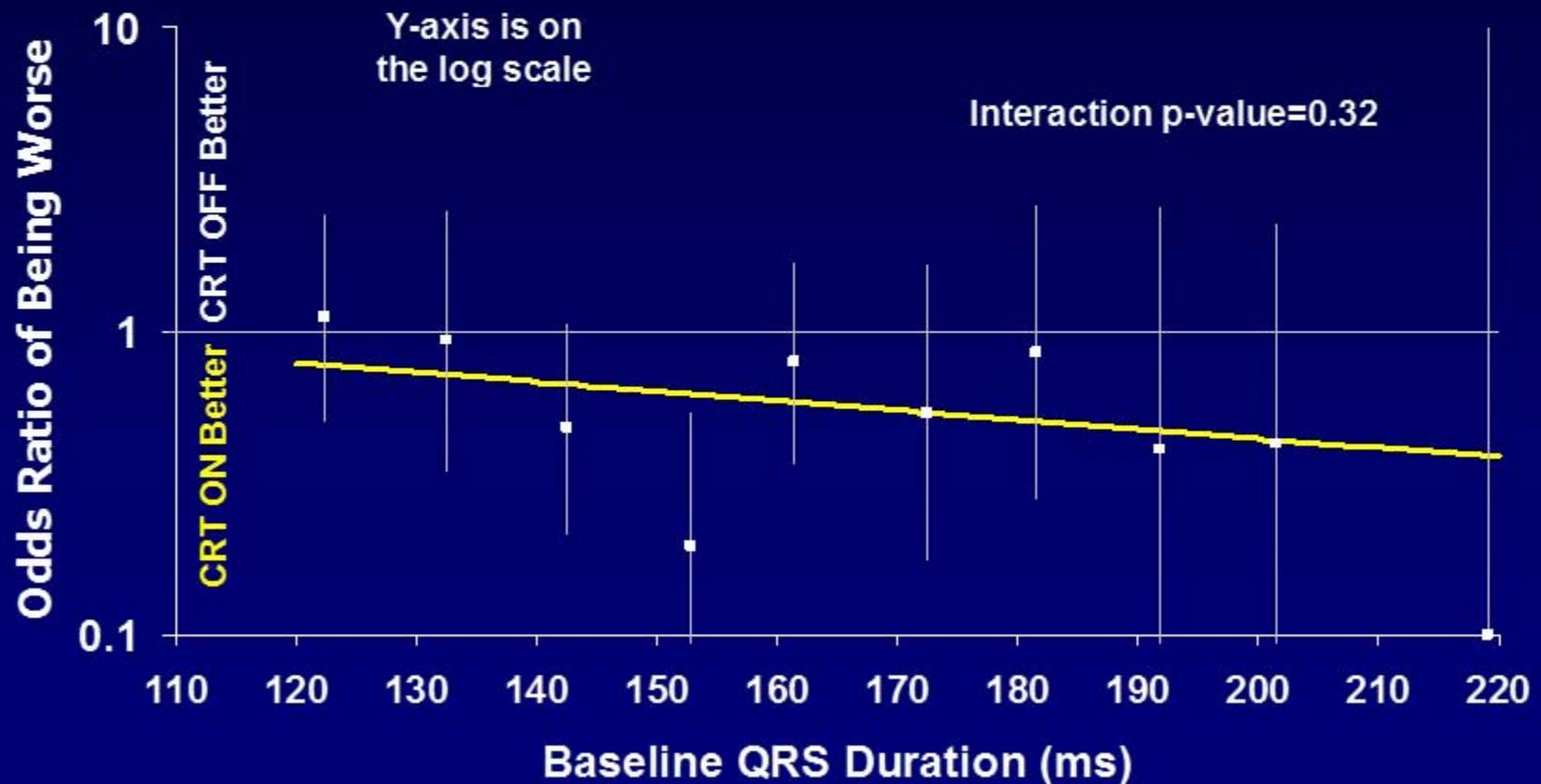


# REVERSE: QRS Duration is a Continuous Variable



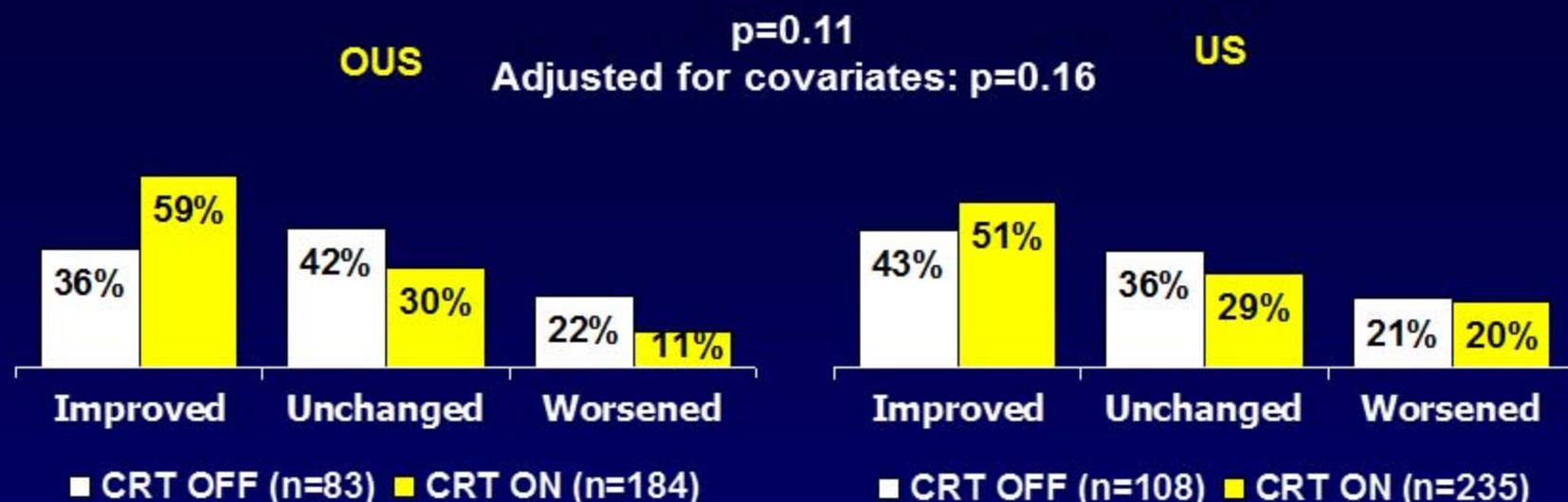
Proportional odds model: QRS duration as a continuous variable

# REVERSE: CRT Beneficial Across QRS Durations for Clinical Composite Response Distribution

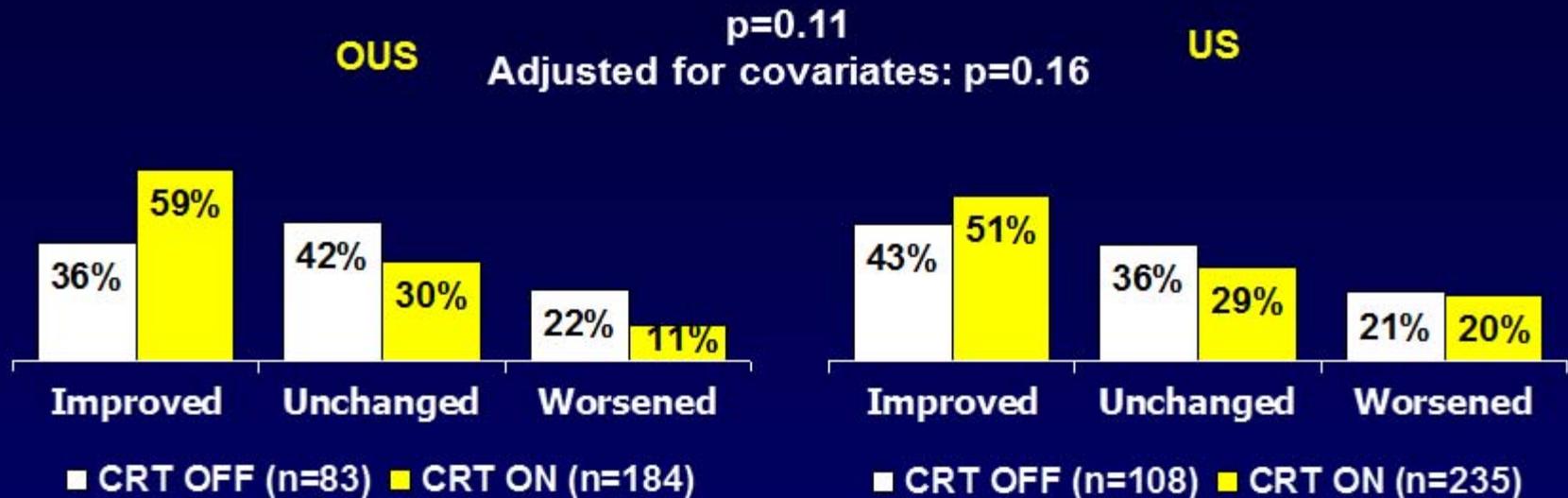


Proportional odds model: QRS duration as a continuous variable

# REVERSE: Consistent Results US and OUS



# REVERSE: Consistent Results US and OUS



Endpoint	US vs. OUS p-value
LVESVi	0.38
HF Hospitalization or Death	0.26
NYHA Class	0.22
Six-minute Hall Walk	0.97
Minnesota QOL	1.00
Kansas City QOL	0.78

# REVERSE: Conclusions

- **Primary endpoint was not met at 12 months (p=0.10)**

# REVERSE: Conclusions

- **Primary endpoint was not met at 12 months (p=0.10)**

**However.....**

- **Totality of data demonstrates that CRT can safely improve mildly symptomatic HF patient outcomes:**
  - **Distribution of clinical composite response**
  - **Reverse remodeling**
  - **Heart failure hospitalization or all-cause death**
  - **LV lead complication rate comparable to other CRT studies**

# **RAFT: Resynchronization/defibrillation for Ambulatory heart Failure Trial**

Tang A, et al. (2010) N Engl J Med 363(25): 2385-2395.

**Anthony Tang, MD**  
***University of British Columbia***  
**RAFT Principal Investigator**  
**RAFT Executive Committee Chair**

# Agenda

- **Study Design**
- **Overall Results**
- **Safety**
- **NYHA Class II Results**
- **Subgroup Results**

# **RAFT: Purpose**

- **To determine whether the addition of CRT to ICD and optimal medical therapy reduces mortality or HF hospitalization, as compared with an ICD and optimal medical therapy,**
  - **NYHA class II or III / systolic dysfunction / wide QRS**
- **Multi-national, randomized, parallel, double-blinded**

# RAFT: Study Design

- **Prospective, randomized, double-blind, multicenter**
  - **1798 enrolled and randomized patients**
  - **34 international centers**
    - **24 Canada, 8 Western Europe, Turkey, 2 Australia**
  - **Randomization 1:1 (ICD : CRT-D)**
- **Enrollment**
  - **January 2003 through February 2009**
- **Follow-up**
  - **40 ± 20 months**

# **RAFT: Study Oversight**

- **Executive Committee**
- **Data and Safety Monitoring Board**
- **Event Committee**
- **Coordinating Center: University of Ottawa Heart Institute**
  - **Database management**
  - **Statistical analysis**

# RAFT: Key Inclusion / Exclusion Criteria

## Inclusion Criteria

- NYHA Class II or III (changed to NYHA Class II only as of February 2006)
- QRS  $\geq$  120 ms or Paced QRS  $\geq$  200 ms
- LVEF  $\leq$  30%
- Optimal medical therapy
- ICD indication
- With or without persistent atrial tachycardia

## Exclusion Criteria

- NYHA Class I or IV
- Existing ICD

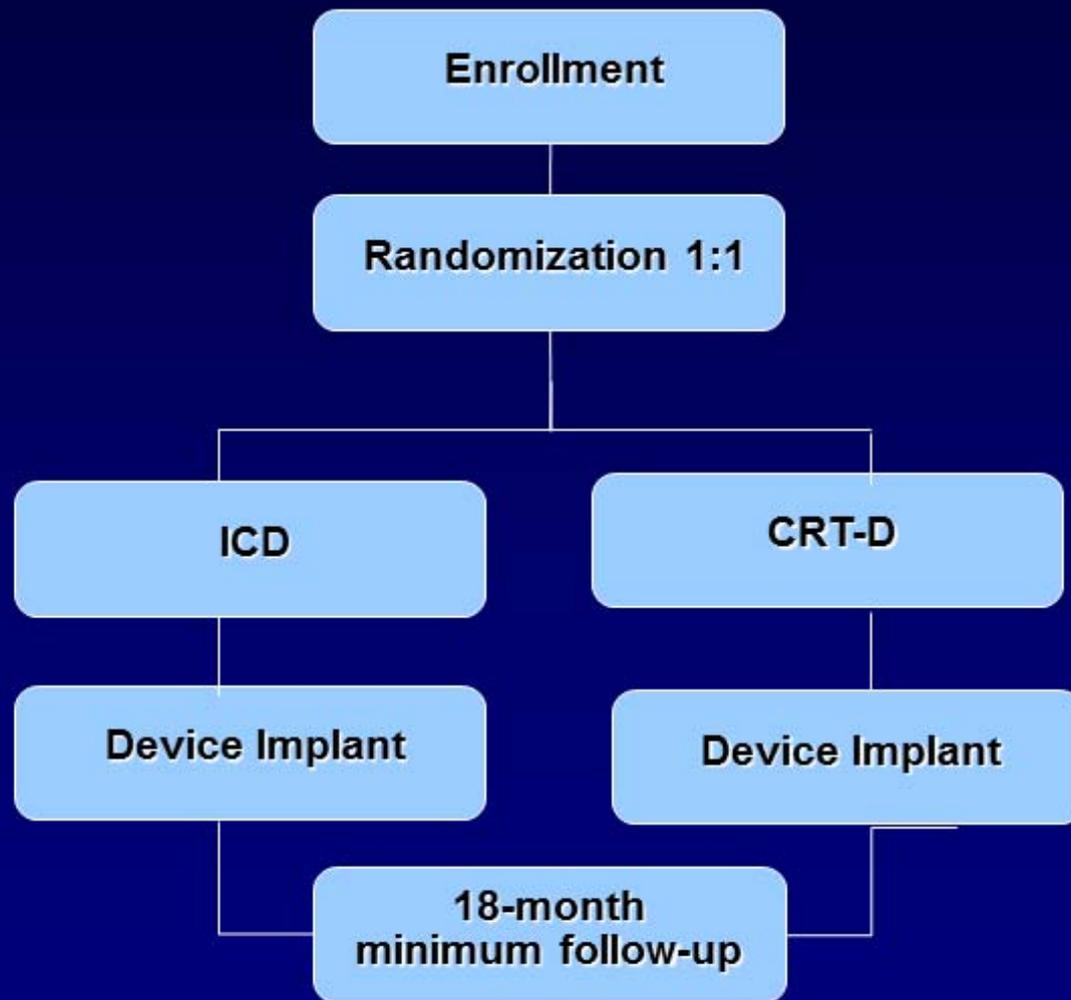
# RAFT: Endpoints

- **Primary Endpoint**
  - **HF hospitalization or all-cause mortality**
- **Key Secondary Endpoint**
  - **Mortality**

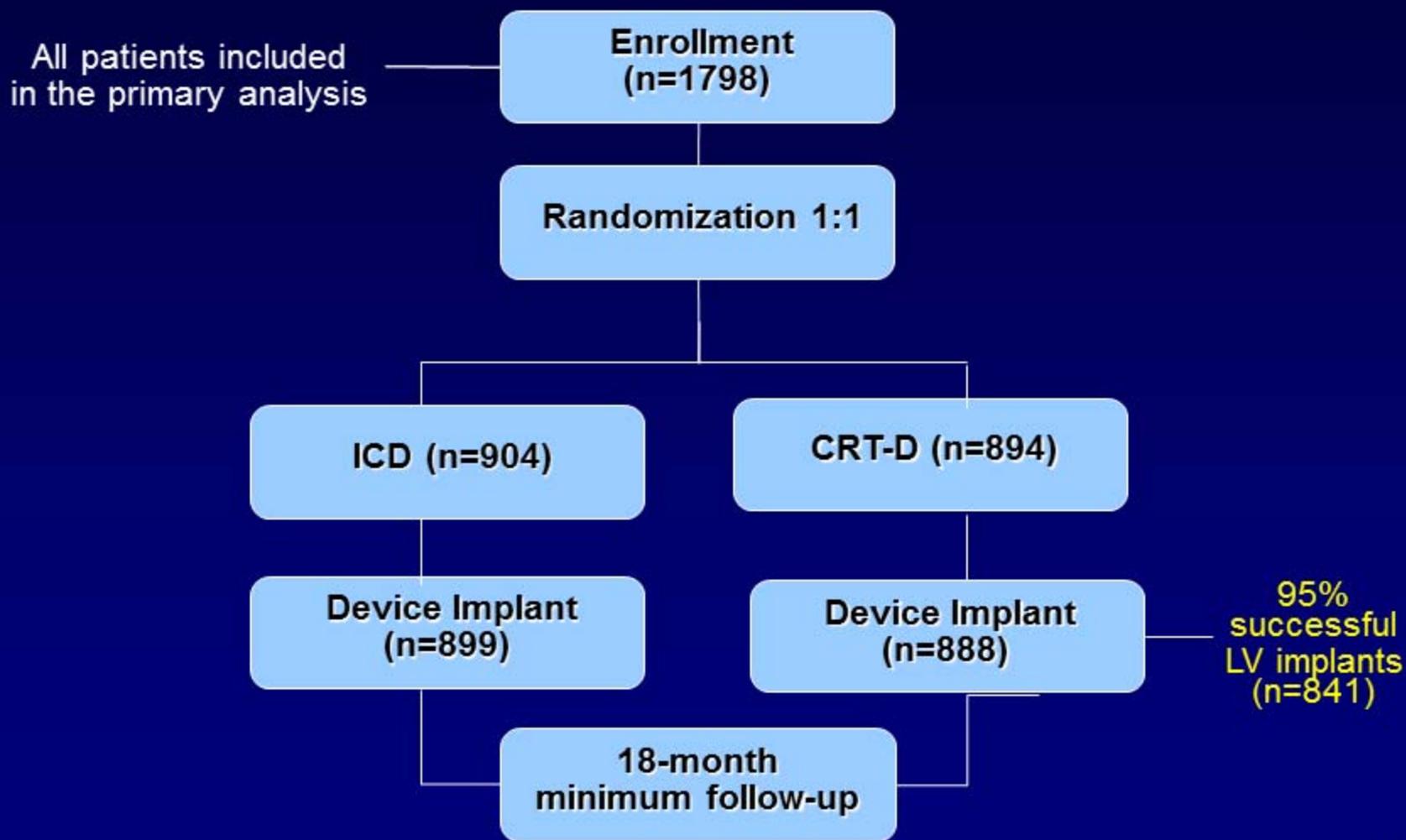
# RAFT: Statistical Methods

- Intention-to-treat
- Two planned interim analyses
- Sample Size Assumptions
  - Primary Endpoint: Time to HF Hosp. or All-Cause Mortality
    - Alpha = 0.05, Power = 85%
    - Annual event rate: CRT-D = 9%; ICD = 13% (25% relative risk reduction)
    - O'Brien–Fleming alpha spending function
    - Sample size = **1800** randomized patients
- NYHA Class II was pre-specified subgroup

# RAFT Study Schematic



# RAFT Study Schematic



Mean follow-up 40 months  $\pm$  20 months

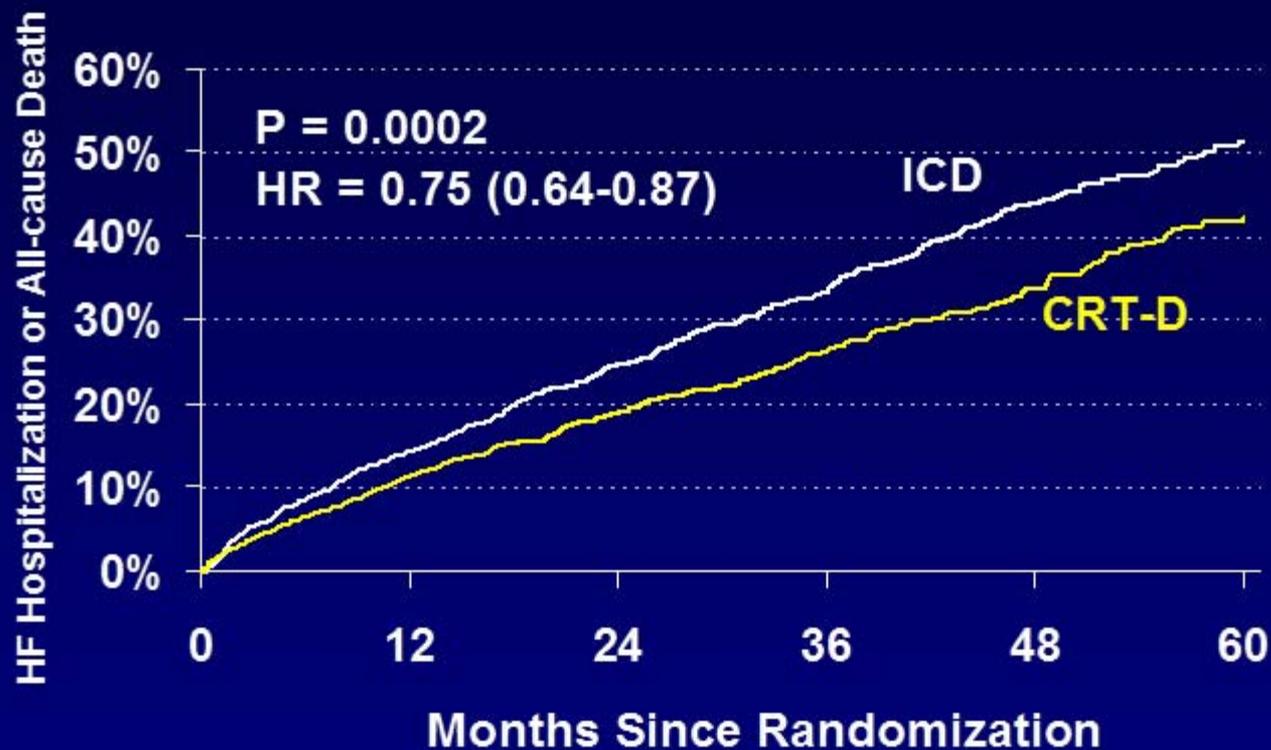
# RAFT: Balanced Distribution of Baseline Characteristics

	ICD n=904	CRT-D n=894	P-value
<b>Age (yrs)</b>	<b>66.2 ± 9.4</b>	<b>66.1 ± 9.3</b>	<b>0.83</b>
<b>Male</b>	<b>81%</b>	<b>85%</b>	<b>0.03</b>
<b>NYHA II</b>	<b>81%</b>	<b>79%</b>	<b>0.41</b>
<b>LVEF (%)</b>	<b>22.6 ± 5.1</b>	<b>22.6 ± 5.4</b>	<b>0.76</b>
<b>QRS (ms)</b>	<b>158 ± 24</b>	<b>157 ± 24</b>	<b>0.28</b>
<b>LBBB</b>	<b>71%</b>	<b>73%</b>	<b>0.40</b>
<b>Ischemic</b>	<b>65%</b>	<b>69%</b>	<b>0.10</b>
<b>Permanent AF</b>	<b>13%</b>	<b>13%</b>	<b>1.00</b>
<b>Beta blockers</b>	<b>89%</b>	<b>90%</b>	<b>0.39</b>
<b>ACE-i/ ARB</b>	<b>97%</b>	<b>96%</b>	<b>0.24</b>

# RAFT: Balanced Distribution of Baseline Characteristics

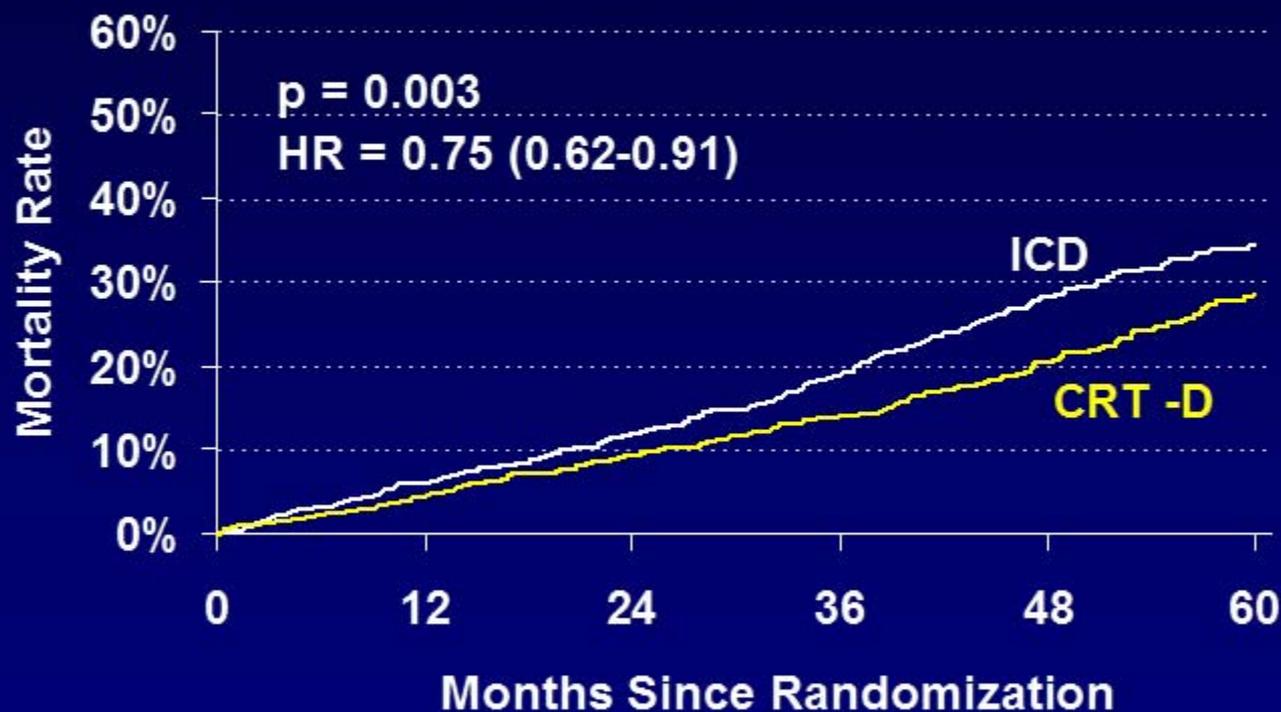
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# RAFT Primary Endpoint: Significant Reduction in HF Hospitalization or All-cause Death



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

# RAFT Secondary Endpoint: Significant Reduction in Mortality



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

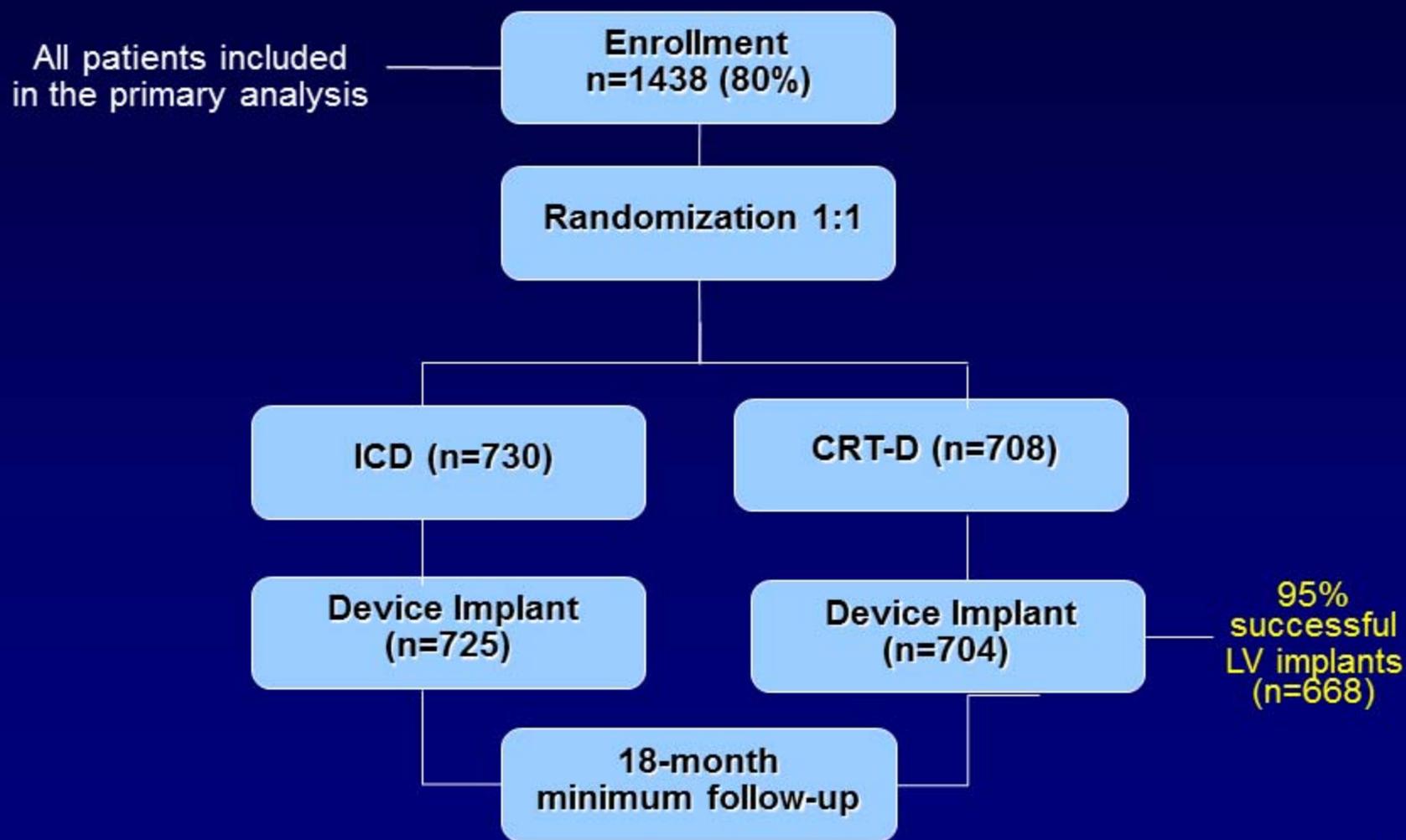
# **RAFT Adverse Events**

- **Adverse event collection**
  - **Procedure or system related complications**
- **RAFT Event Committee classified:**
  - **Complication**
    - **Invasive intervention or**
    - **Termination of significant device function**

# RAFT Safety: Left Ventricular Lead Complication Rate Similar to REVERSE

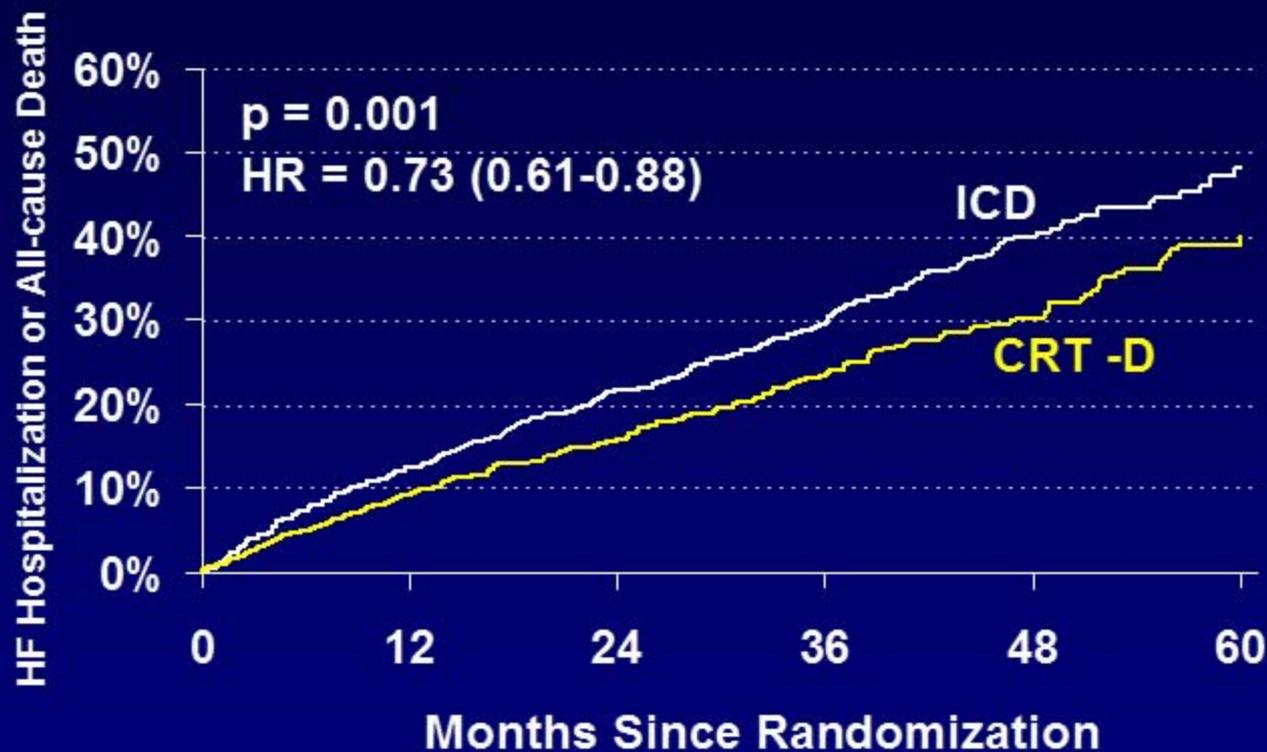


# RAFT NYHA Class II: Enrollment and Randomization



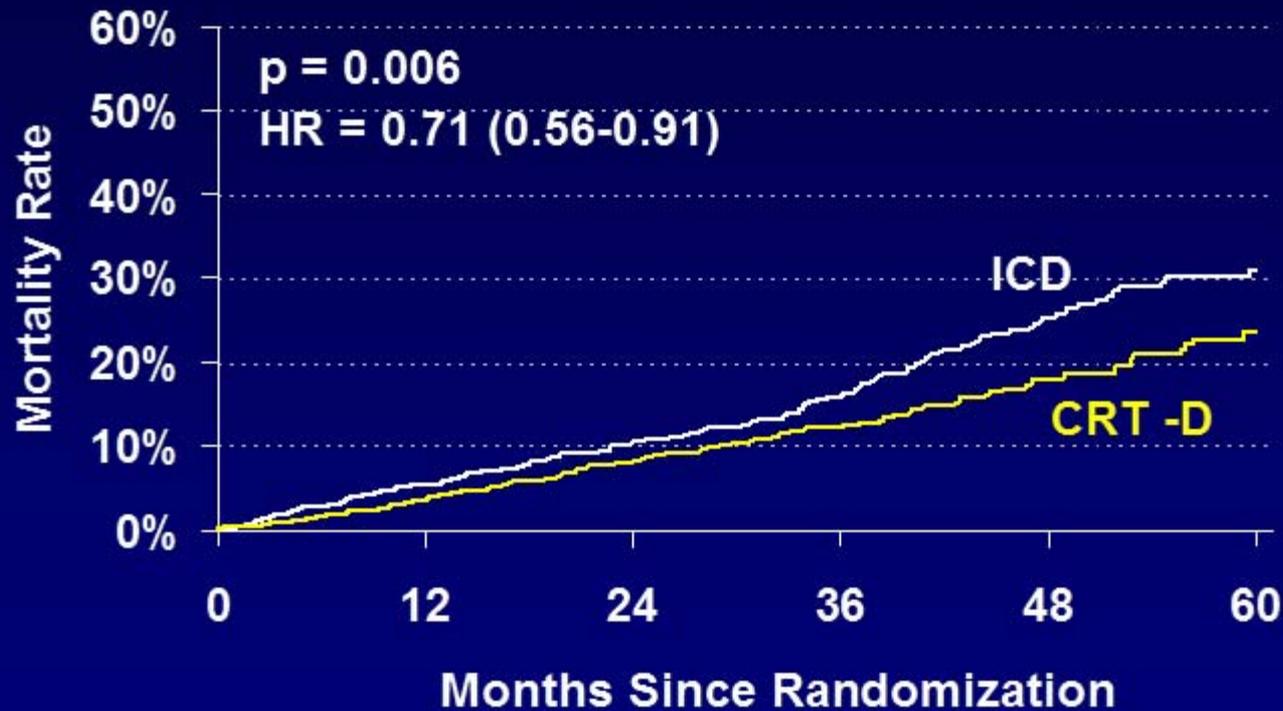
Mean follow-up 40 months  $\pm$  20 months

# RAFT NYHA Class II: Significant Reduction in HF Hospitalization or All-cause Mortality



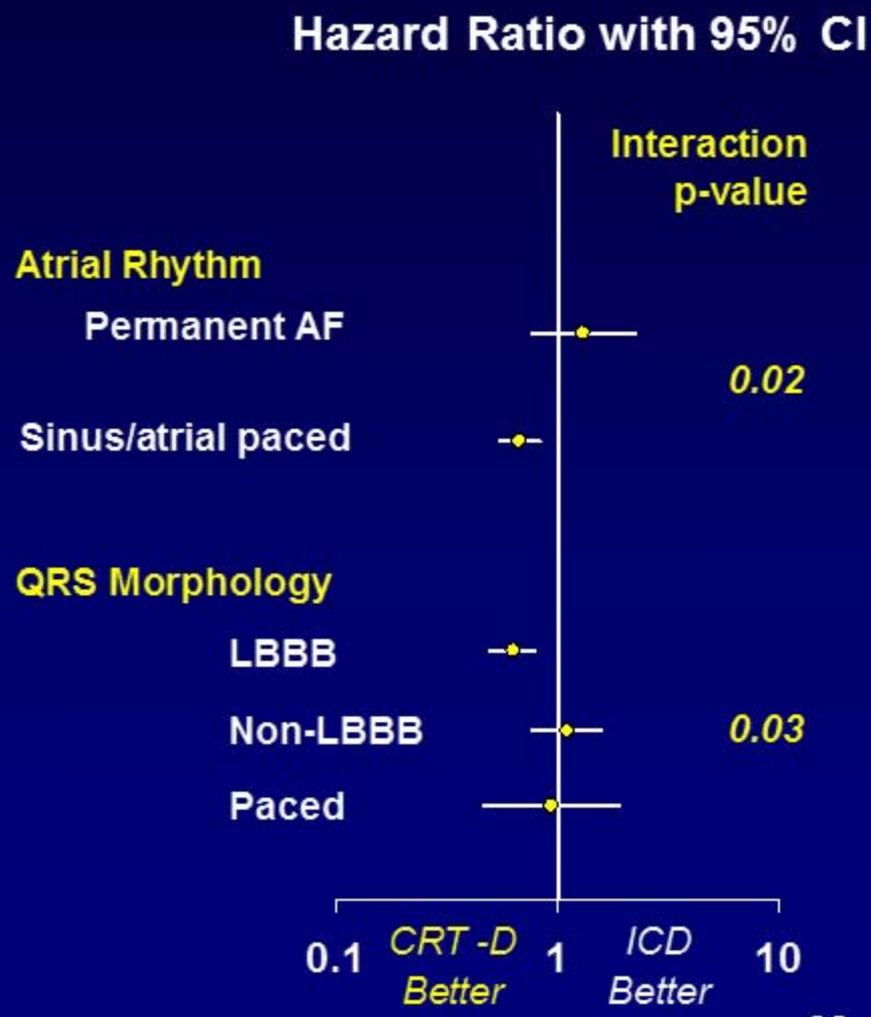
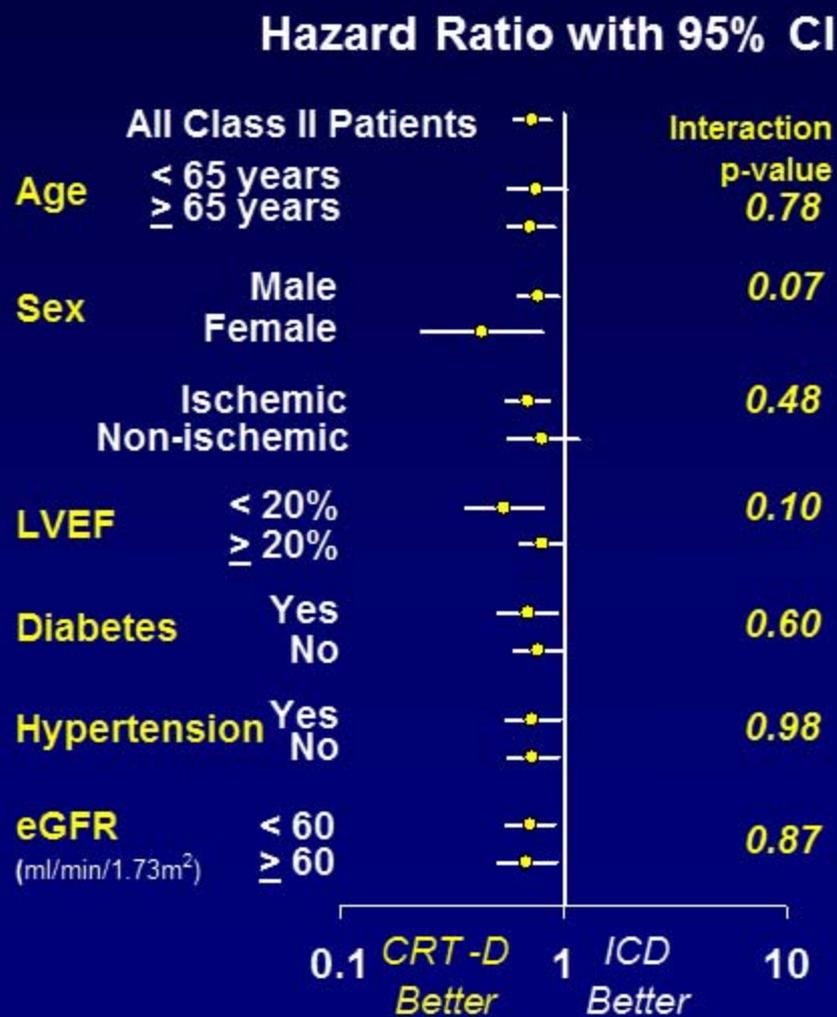
Number	730	638	465	299	146	57
remaining	708	640	488	315	181	70

# RAFT NYHA Class II: Significant Reduction in Mortality

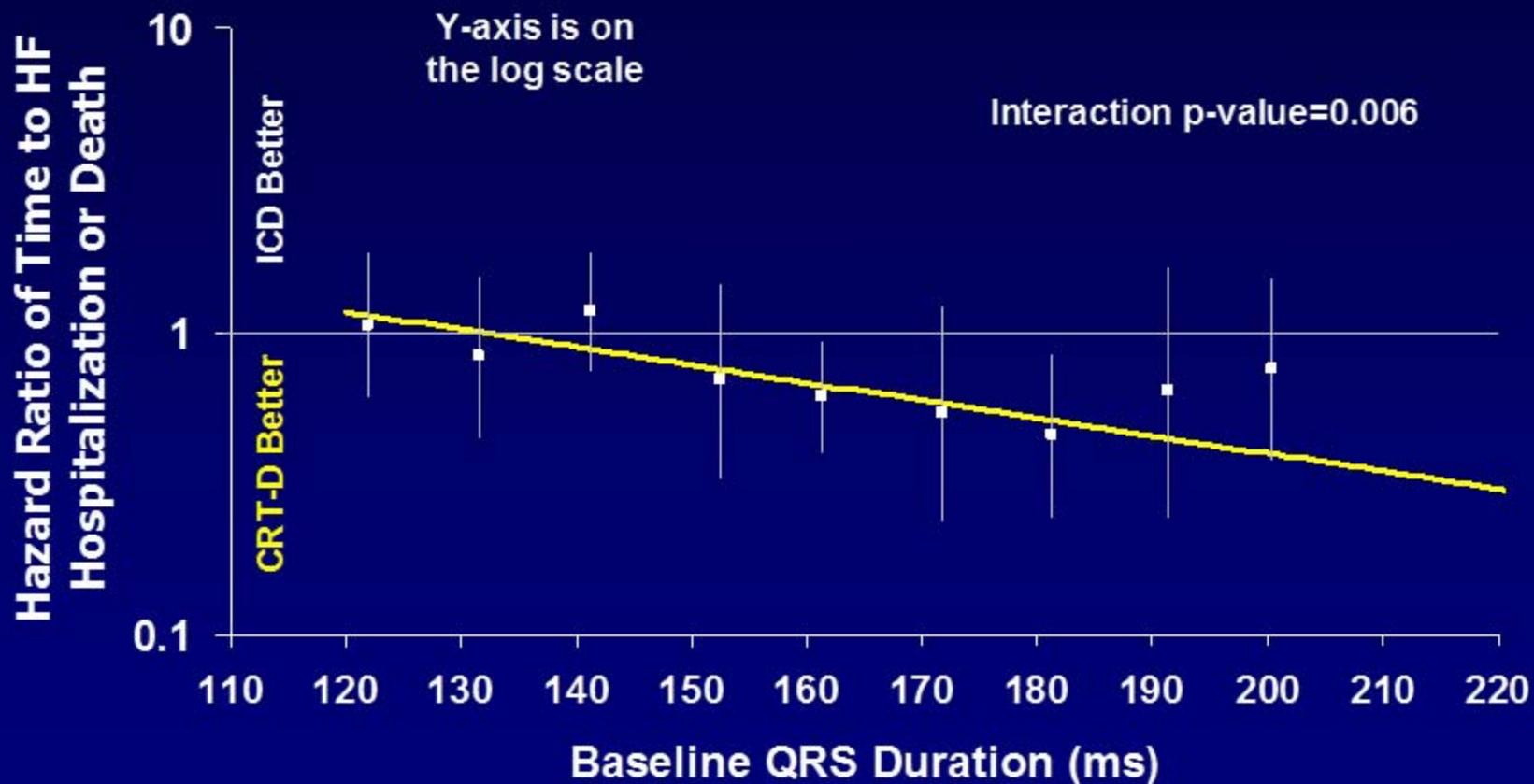


Number	730	687	533	366	189	83
remaining	708	679	530	361	206	89

# RAFT NYHA Class II Subgroup Analysis: HF Hospitalization or All-cause Mortality



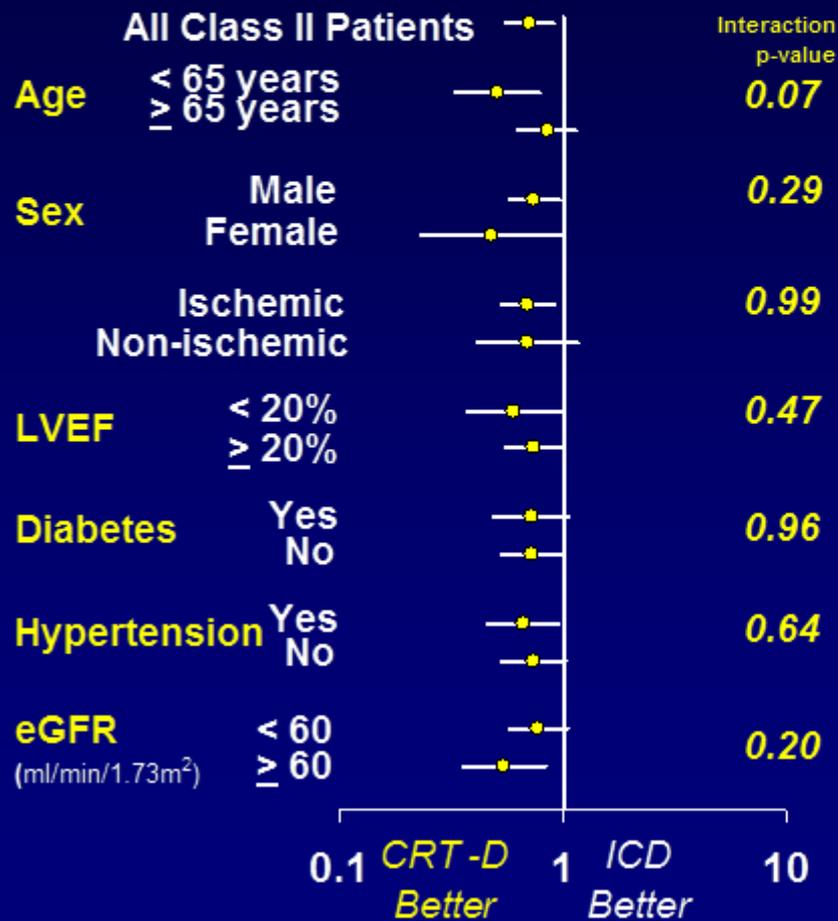
# RAFT NYHA Class II: CRT Beneficial Across QRS Durations for HF Hospitalization or All-cause Death



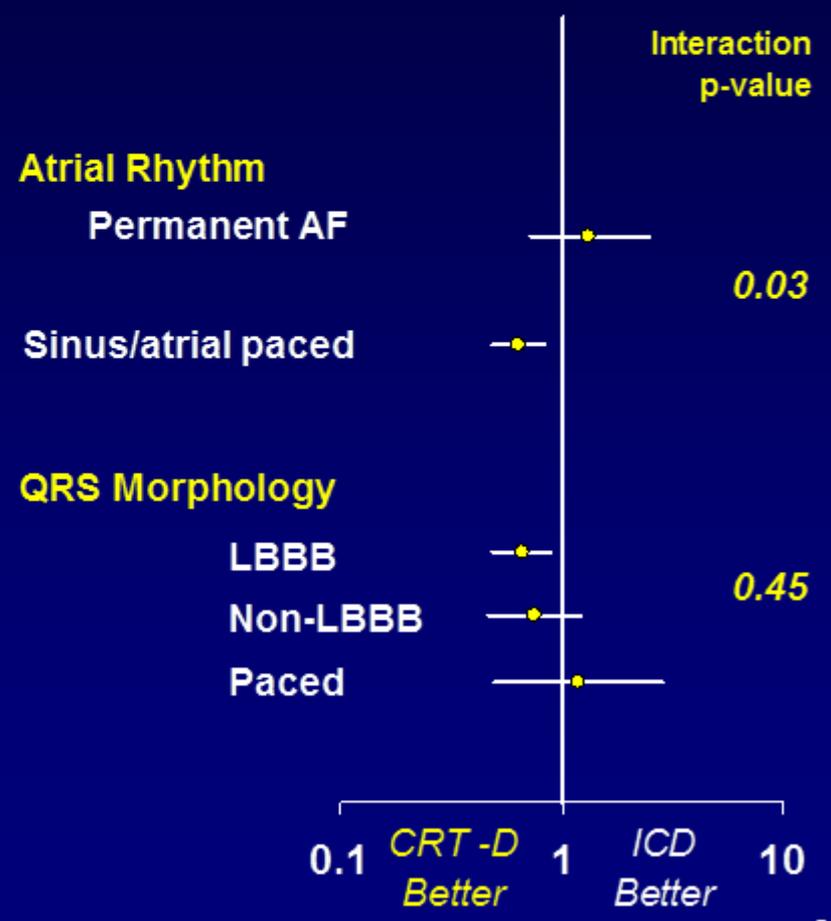
Proportional odds model: QRS duration as a continuous variable

# RAFT NYHA Class II Subgroup Analysis: Mortality

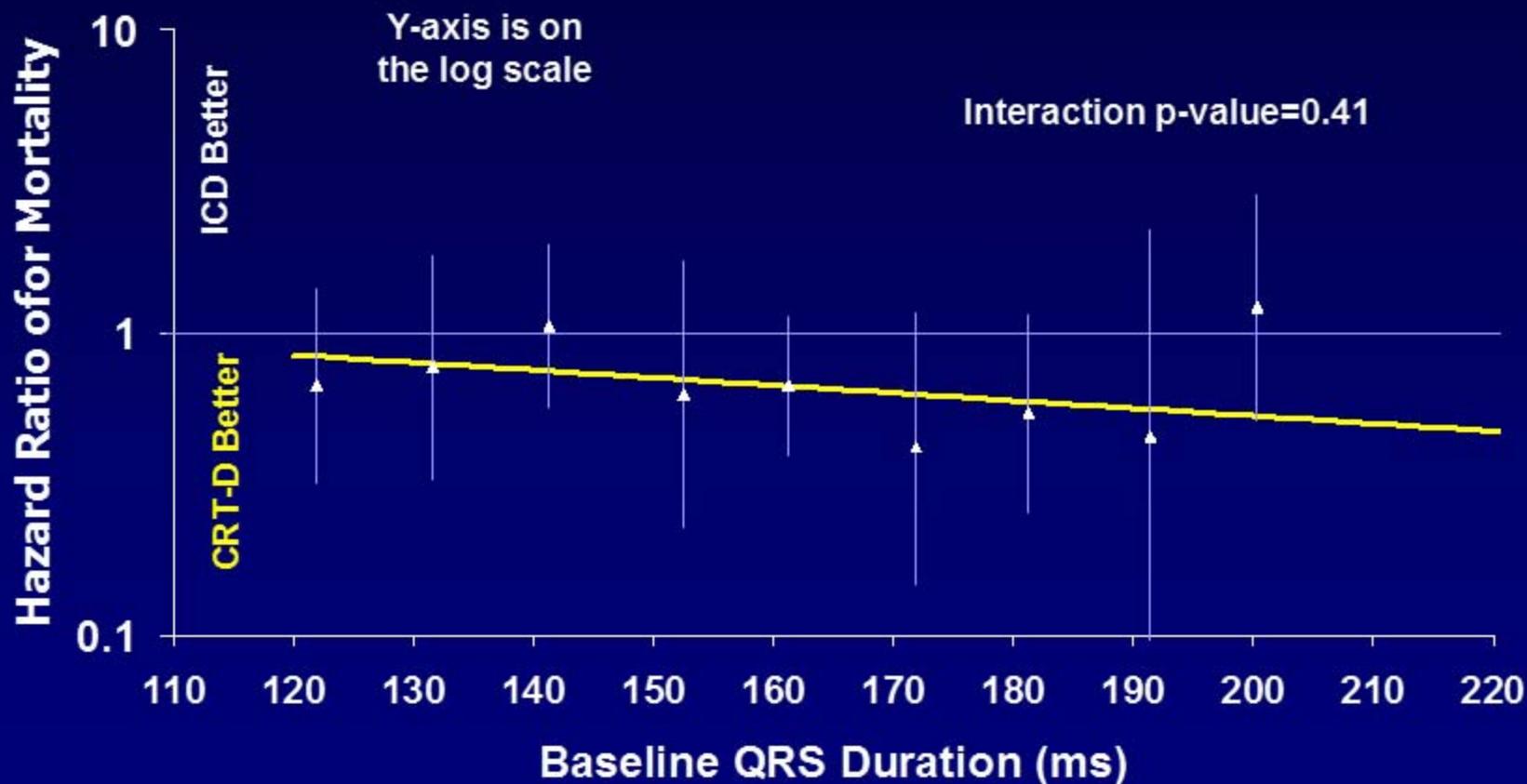
Hazard Ratio with 95% CI



Hazard Ratio with 95% CI



# RAFT NYHA Class II: CRT Beneficial Across All QRS Durations for Mortality



Proportional odds model: QRS duration as a continuous variable

## **RAFT Conclusions**

- **Among ICD-indicated patients with mildly symptomatic HF / systolic dysfunction / QRS prolongation, CRT-D:**
  - **Reduces heart failure hospitalization or all-cause mortality**
  - **Reduces mortality alone**
- **Findings support expanded use of CRT-D in mildly symptomatic heart failure**

# **Totality of the Evidence**

**William T. Abraham, MD, FACP, FACC, FAHA**  
*The Ohio State University*  
**REVERSE Steering Committee**

# Agenda

- **Landscape of CRT in mildly symptomatic heart failure**
- **Comparison of REVERSE and RAFT Proposed Patient Population Results**
- **Risk/Benefit profile in mildly symptomatic population**

# More Than a Decade of Experience With CRT in Mildly Symptomatic Heart Failure

2010: RAFT  
Average 40 months,  
n=1438

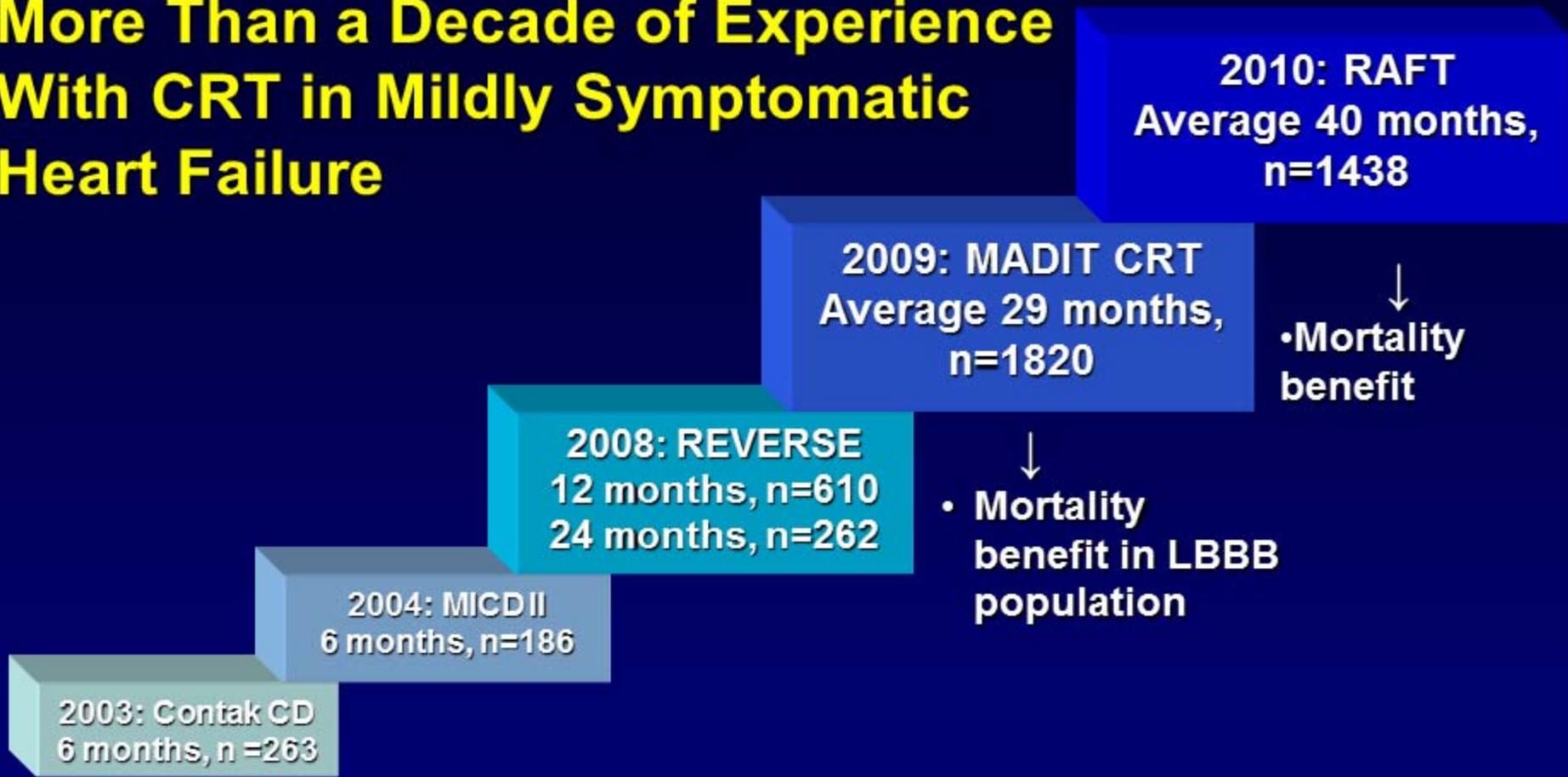
2009: MADIT CRT  
Average 29 months,  
n=1820

2008: REVERSE  
12 months, n=610  
24 months, n=262

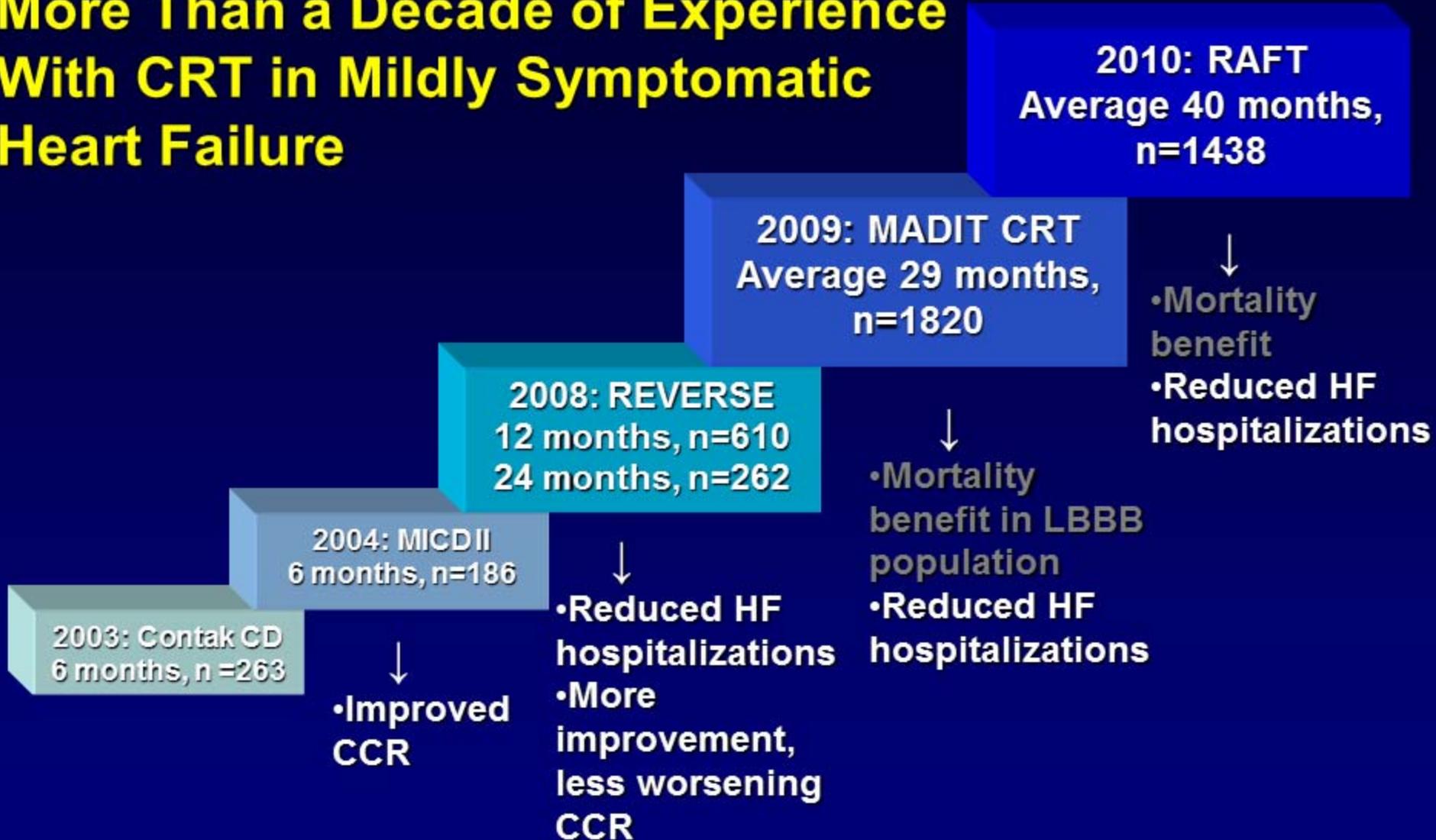
2004: MICDII  
6 months, n=186

2003: Contak CD  
6 months, n =263

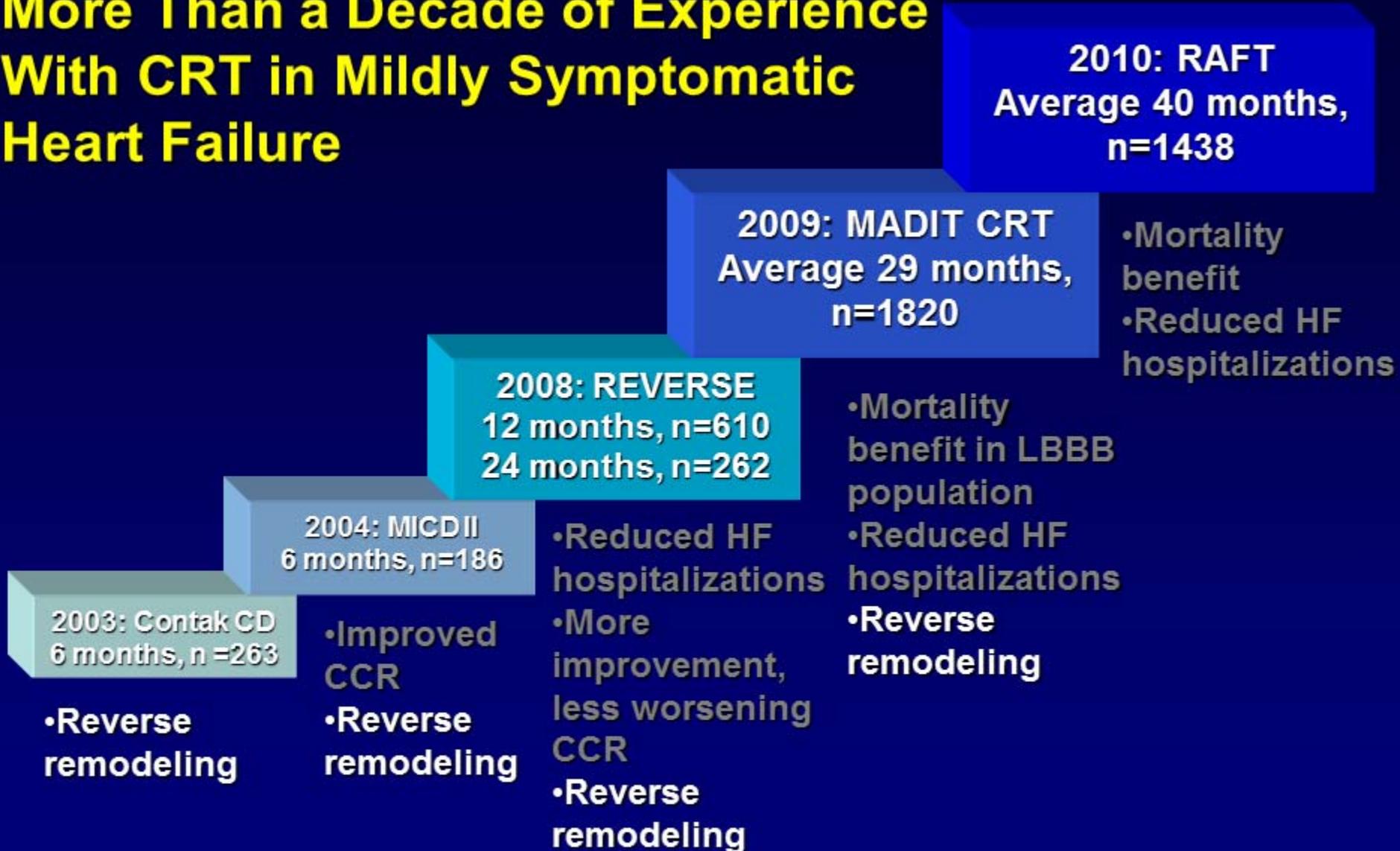
# More Than a Decade of Experience With CRT in Mildly Symptomatic Heart Failure



# More Than a Decade of Experience With CRT in Mildly Symptomatic Heart Failure



# More Than a Decade of Experience With CRT in Mildly Symptomatic Heart Failure



Contak CD: Higgins et al. JACC 2003;42:1454-9.

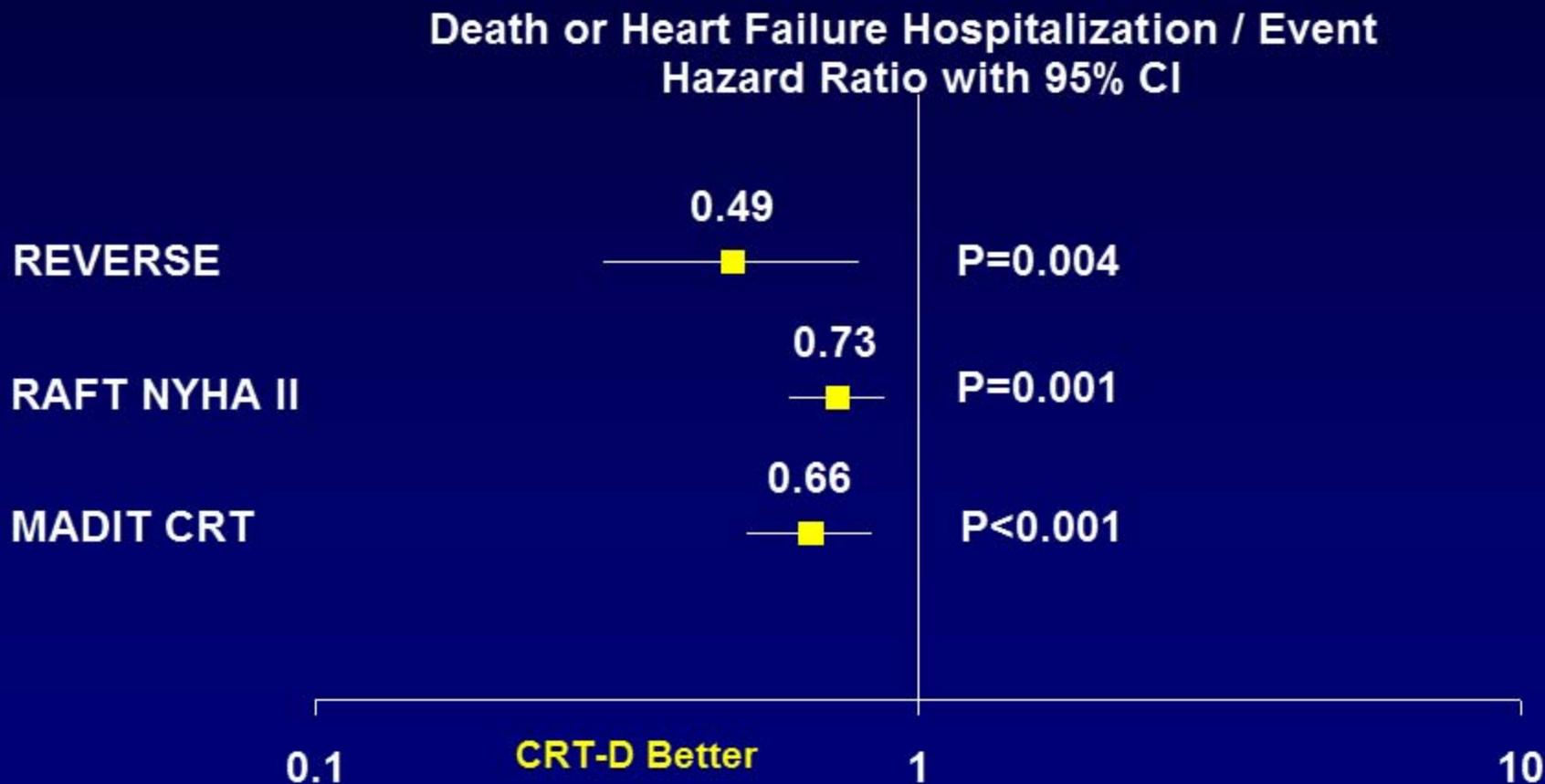
MICD II: Abraham et al. Circulation 2004;110:2864-8.

MADIT-CRT: Moss AJ, et al. N Engl J Med 2009; 361(14): 1329-38

# Complementary Study Designs

	REVERSE	RAFT
<b>Study design</b>	Randomized 2:1 CRT±D ON vs OFF Double-blinded	Randomized 1:1 CRT-D vs ICD Double-blinded
<b>Size</b>	610 randomized U.S., Canada, Europe	1798 randomized Canada, Western Europe, Turkey, Australia
<b>Randomized Duration</b>	12 months (US, Canada) 24 months (Europe)	18 months minimum; Mean 40 months
<b>Primary endpoint</b>	HF Clinical Composite (proportion worsened)	Total mortality + HF hospitalization
<b>NYHA Class</b>	I and II (ACC/AHA Stage C)	II and III

# Concordant Results for CRT in Patients with Mild Symptoms



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

RAFT: Tang A, et al. NEJM 2010;363: 2385-95.

MADIT-CRT: Moss AJ, et al. N Engl J Med 2009; 361(14): 1329-38.

## Proposed Patient Population

- ✓ CRT-D (ICD-indicated)
- ✓ NYHA Class II
- ✓ LVEF  $\leq 30\%$
- ✓ QRS  $\geq 120$  ms
- ✓ Left Bundle Branch Block

# Proposed Patient Population Based on Common Inclusion Criteria

	REVERSE	RAFT	Proposed
CRT Device	CRT-D; CRT-P	CRT-D	<b>CRT-D</b>
NYHA	I and II	II and III	<b>II</b>
LVEF (%)	≤ 40%	≤ 30%	<b>≤ 30%</b>
Permanent AF	No	Yes	<b>No</b>
Permanent Pacing	No	Yes	<b>No</b>
QRS (ms)	≥ 120	≥ 120	<b>≥ 120</b>

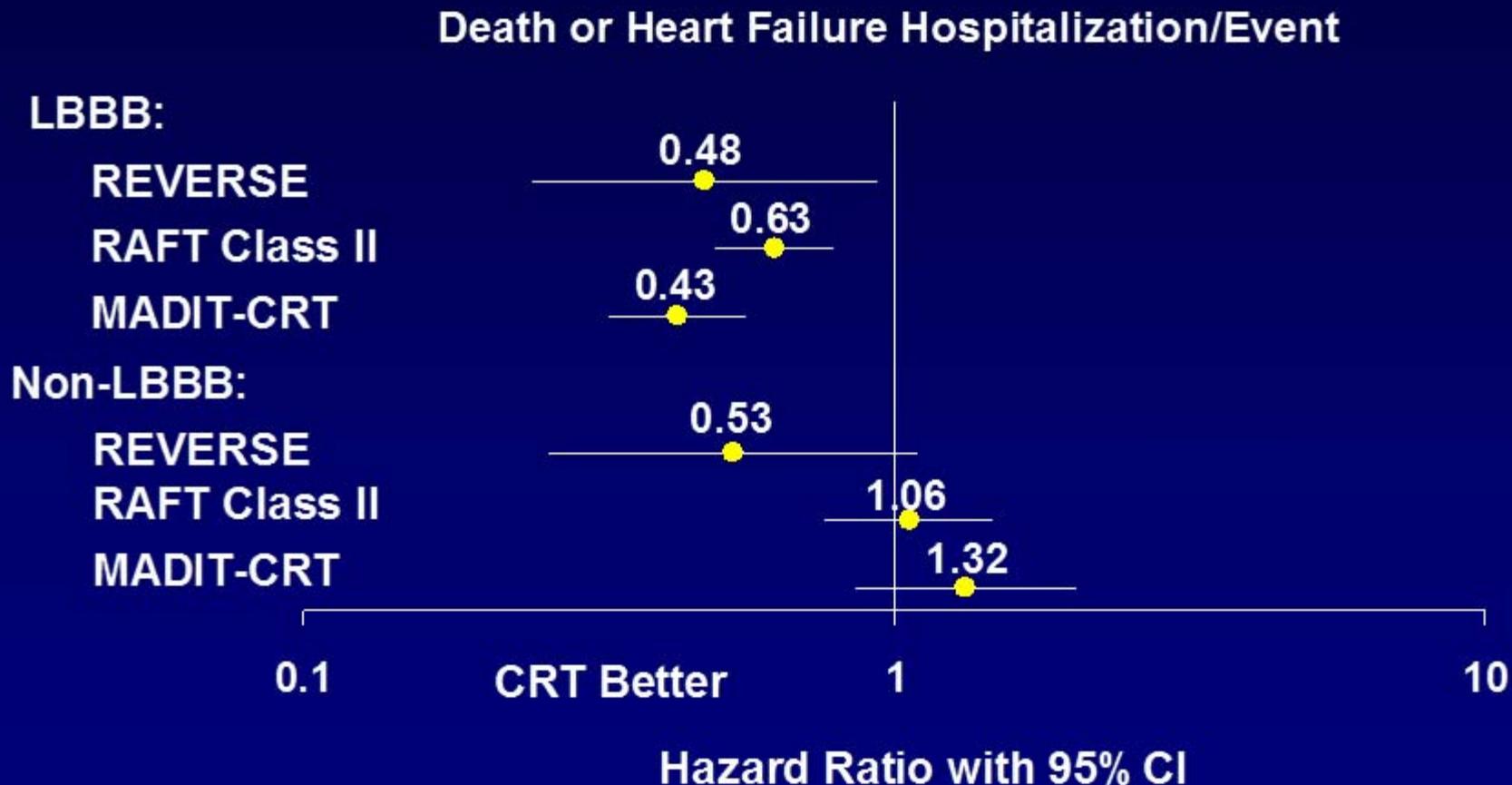
# Proposed Patient Population Further Refined to Left Bundle Branch Block Morphology

	REVERSE	RAFT	Proposed
CRT Device	CRT-D; CRT-P	CRT-D	CRT-D
NYHA	I and II	II and III	II
LVEF (%)	≤ 40%	≤ 30%	≤ 30%
Permanent AF	No	Yes	No
Permanent Pacing	No	Yes	No
QRS (ms)	≥ 120	≥ 120	≥ 120
QRS Morphology	All	All	LBBB

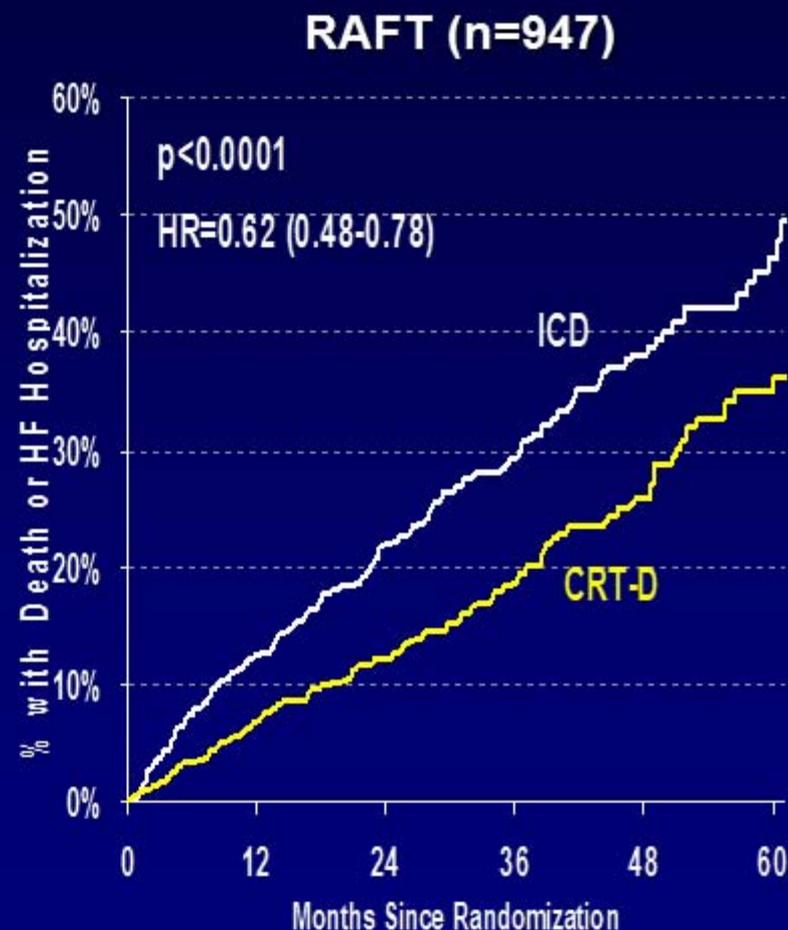
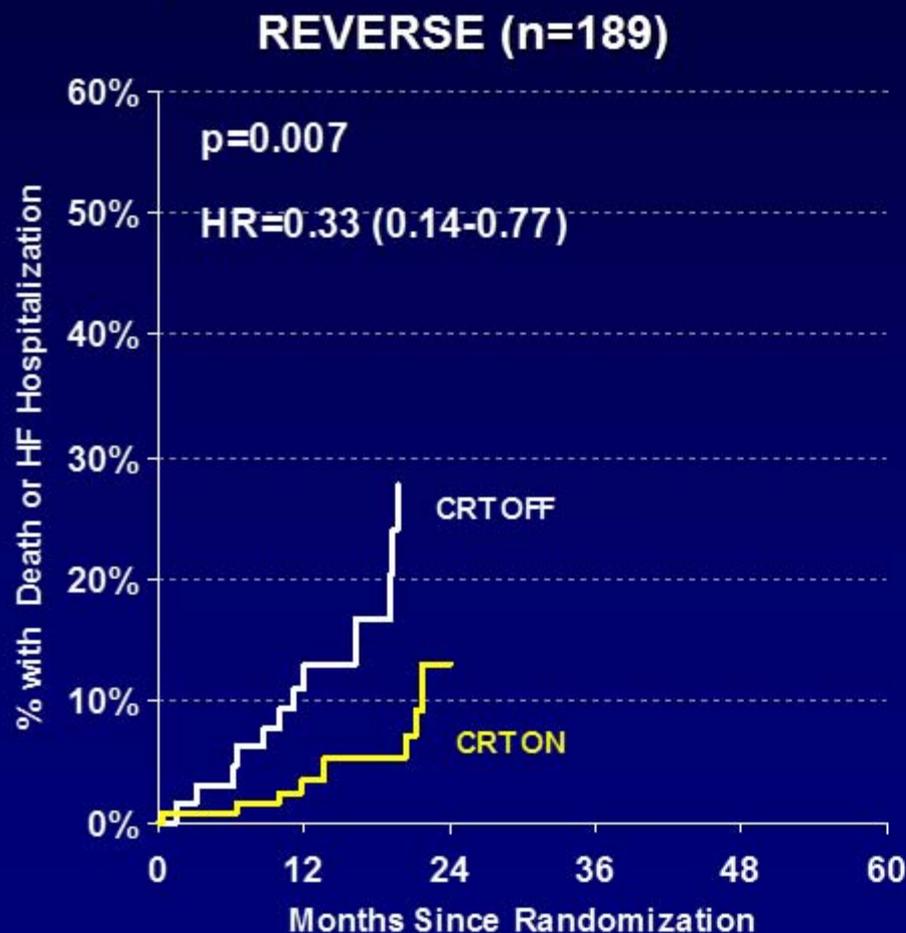
# Proposed Patient Population Similar to Existing Precedent

	<b>REVERSE</b>	<b>RAFT</b>	<b>Proposed</b>	<b>MADIT-CRT</b>
<b>CRT Device</b>	<b>CRT-D; CRT-P</b>	<b>CRT-D</b>	<b>CRT-D</b>	<b>CRT-D</b>
<b>NYHA</b>	<b>I and II</b>	<b>II and III</b>	<b>II</b>	<b>I (ischemic), II</b>
<b>LVEF (%)</b>	<b>≤ 40%</b>	<b>≤ 30%</b>	<b>≤ 30%</b>	<b>≤ 30%</b>
<b>Permanent AF</b>	<b>No</b>	<b>Yes</b>	<b>No</b>	<b>No</b>
<b>Permanent Pacing</b>	<b>No</b>	<b>Yes</b>	<b>No</b>	<b>No</b>
<b>QRS (ms)</b>	<b>≥ 120</b>	<b>≥ 120</b>	<b>≥ 120</b>	<b>≥ 130</b>
<b>QRS Morphology</b>	<b>All</b>	<b>All</b>	<b>LBBB</b>	<b>LBBB</b>

# Consistent Benefit of CRT for Patients with LBBB within Study Cohorts



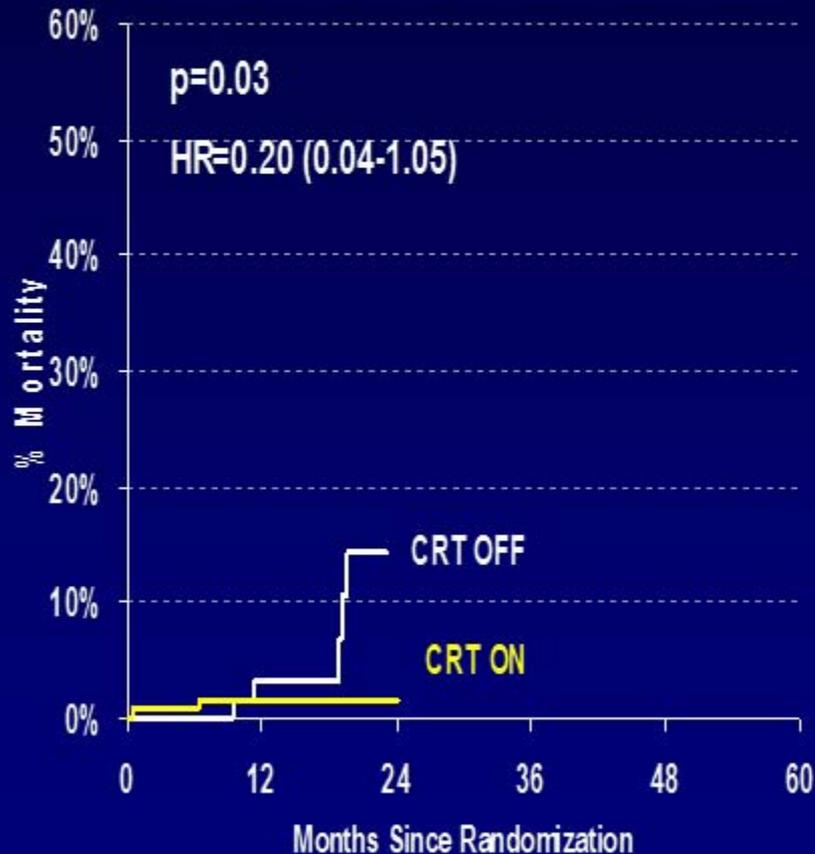
# REVERSE and RAFT: HF Hospitalization or All-cause Mortality in Proposed Patient Population\*



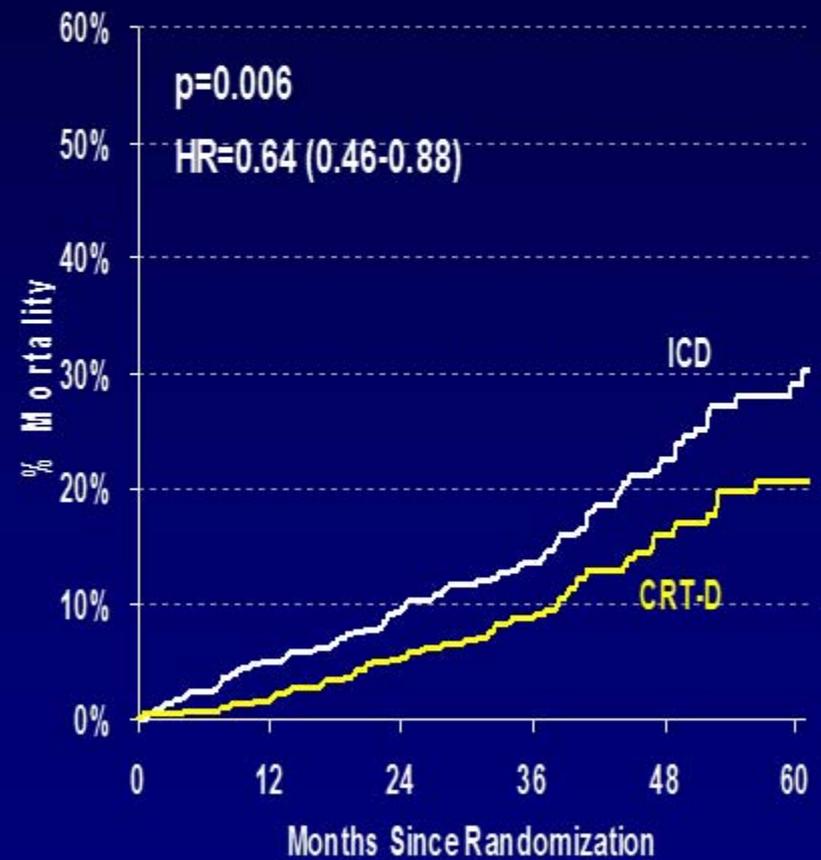
\* NYHA Class II, LVEF  $\leq 30\%$ , LBBB, QRS  $\geq 120$  ms

# REVERSE and RAFT: Mortality in the Proposed Patient Population\*

REVERSE (n=189)



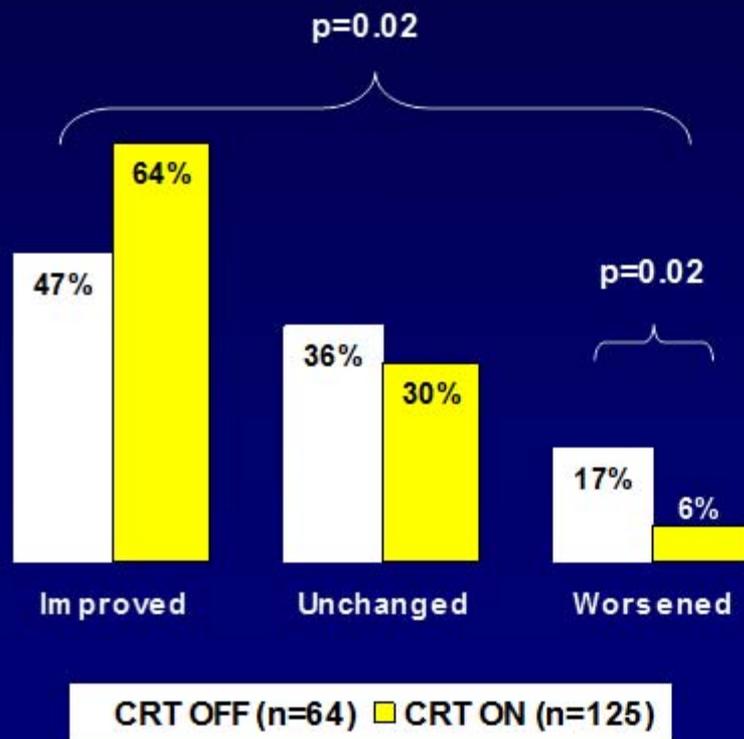
RAFT (n=947)



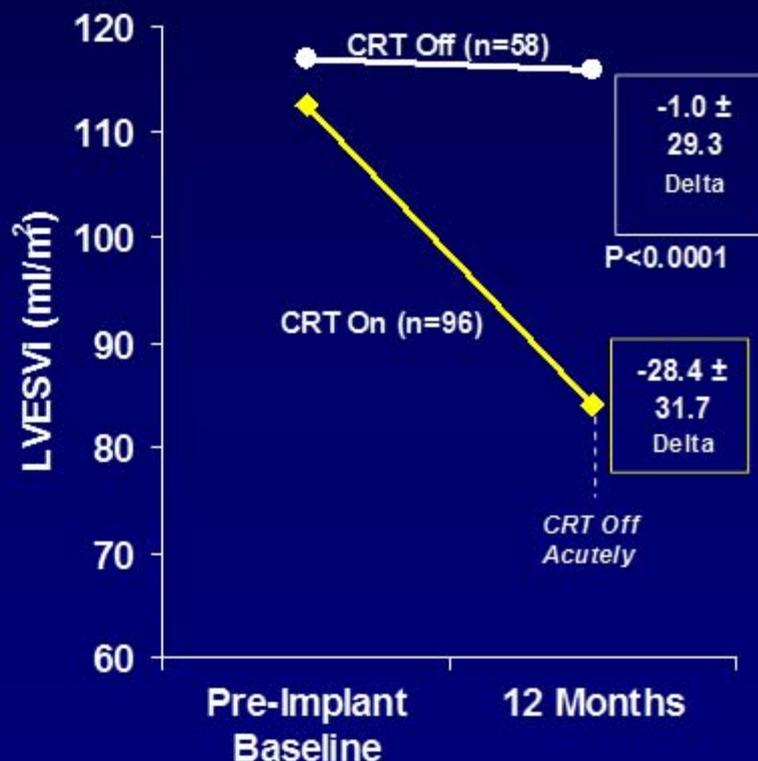
\* NYHA Class II, LVEF  $\leq$  30%, LBBB, QRS  $\geq$  120 ms

# REVERSE: Proposed Patient Population\* Results for Key Endpoints at 12 Months (CCR and LVESVi)

## Clinical Composite Response



## LVESVi



\* NYHA Class II, LVEF  $\leq$  30%, QRS  $\geq$  120 ms, LBBB

# Risk / Benefit Profile for Proposed Population

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<b>Significant morbidity benefit</b>	<b>38% reduction in HF hosp. or all-cause death<sup>1</sup></b>
<b>Significant mortality benefit</b>	<b>36% mortality reduction<sup>1</sup></b>
<b>Significant reverse remodeling</b>	<b>25% LVESVi reduction<sup>2</sup></b>

---

1. RAFT proposed patient population

2. REVERSE proposed patient population

## LV Lead Complication Rate Comparable to Other Medtronic CRT Studies

Study	Enrollment Period	12-month LV Lead Complication Rate
RAFT (CRT-D group)	2003 - 2009	7.4%
REVERSE	2004 - 2006	9.1%
Concerto AT	2006	9.9%
MIRACLE ICD	1999 - 2001	16.3%
MIRACLE	1998 - 2000	10.1%

# **Totally of Evidence: Conclusion**

- **In the proposed patient population, CRT-D:**
  - **Reduces mortality**
  - **Reduces heart failure hospitalization**
  - **Improves cardiac function**

# **Perspective on FDA Concerns**

**Marshall Stanton, MD**  
**Vice President, Clinical Research**  
**Medtronic Cardiac and Vascular Group**

# **REVERSE Poolability by Geography**

## REVERSE Showed No Significant Outcome Differences between US and OUS

Outcome	Entire Cohort Interaction p-value	Proposed Population Interaction p-value
Clinical Composite Response	0.11	0.50
Change in LVESVi	0.38	0.93
Time to First HF Hospitalization or Death	0.26	0.87

- Difference in interaction p-value between entire and proposed cohorts driven by QRS morphology
  - Larger percentage of non-LBBB subjects in the U.S.

# Proposed Population

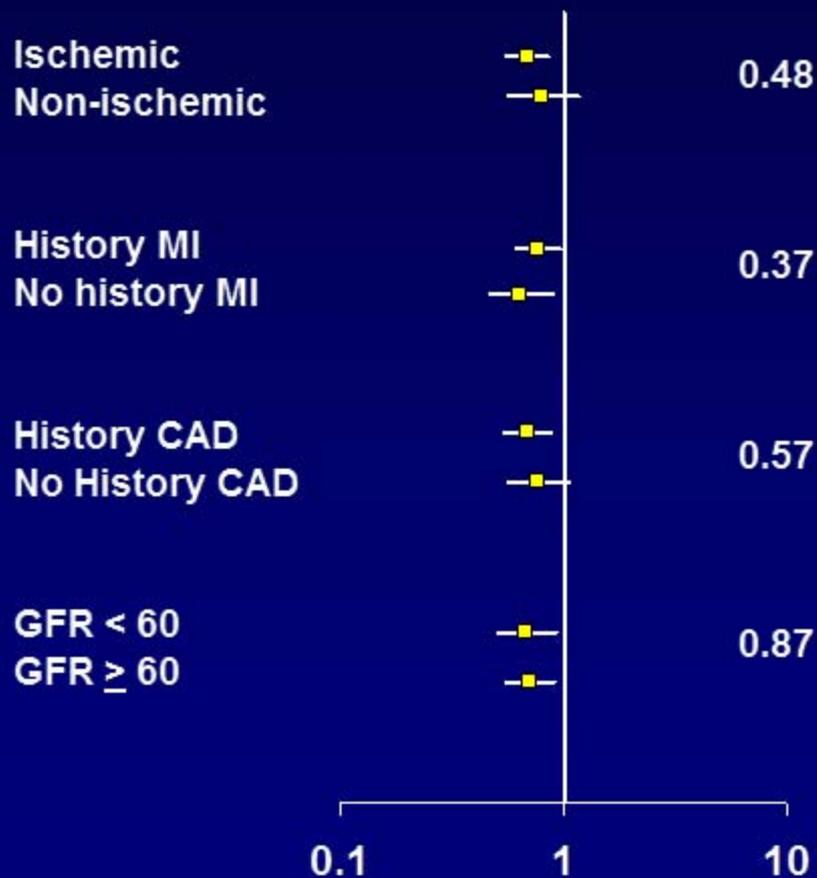
# Conservative Approach Used in Identifying Proposed Patient Population

	REVERSE	RAFT	Proposed
CRT Device	CRT-D; CRT-P	CRT-D	CRT-D
NYHA	I and II	II and III	II
LVEF (%)	≤ 40%	≤ 30%	≤ 30%
Permanent AF	No	Yes	No
Permanent Pacing	No	Yes	No
QRS (ms)	≥ 120	≥ 120	≥ 120
QRS Morphology	All	All	LBBB

# **RAFT NYHA Class II Population**

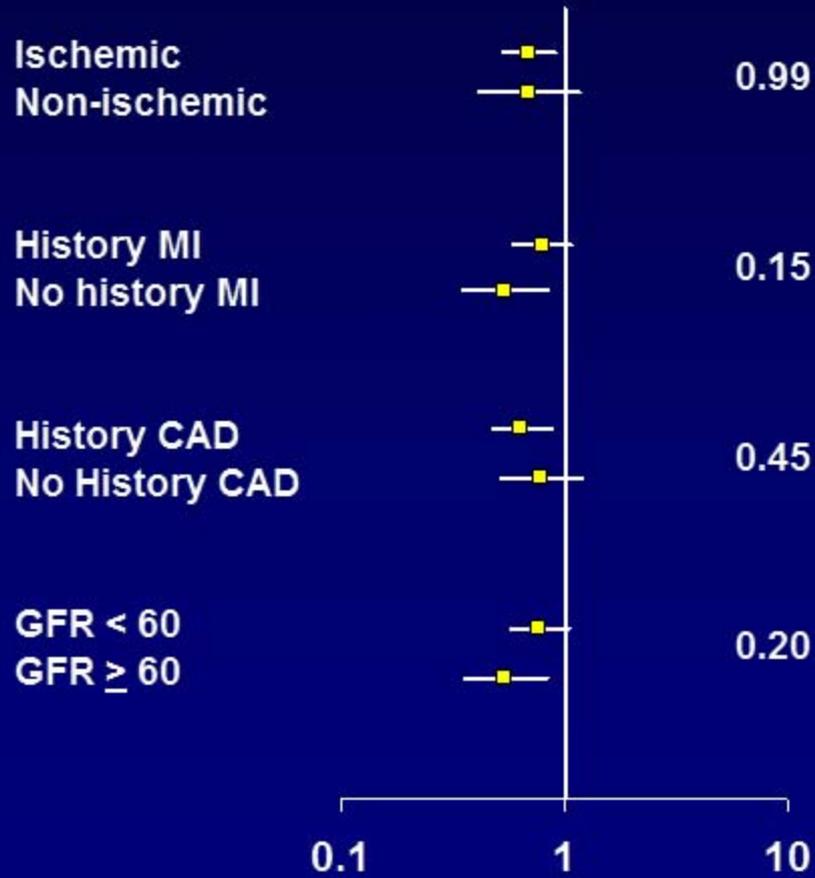
# RAFT NYHA II: Co-morbidity Patient Analysis

**HF Hospitalization or Death  
Hazard Ratio with 95% CI**



**CRT-D Better**      **ICD Better**

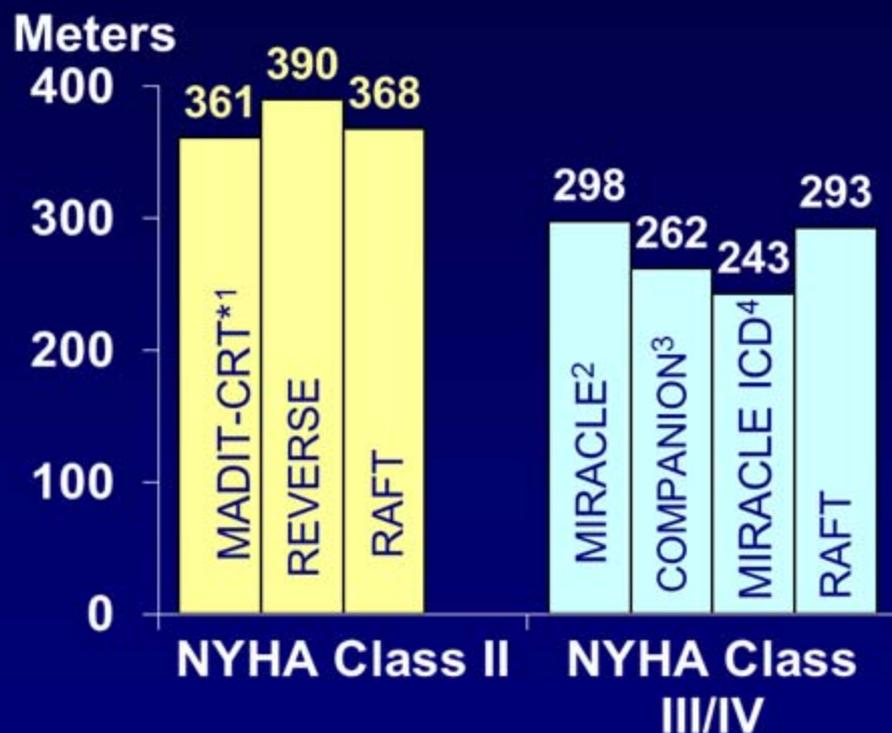
**Mortality  
Hazard Ratio with 95% CI**



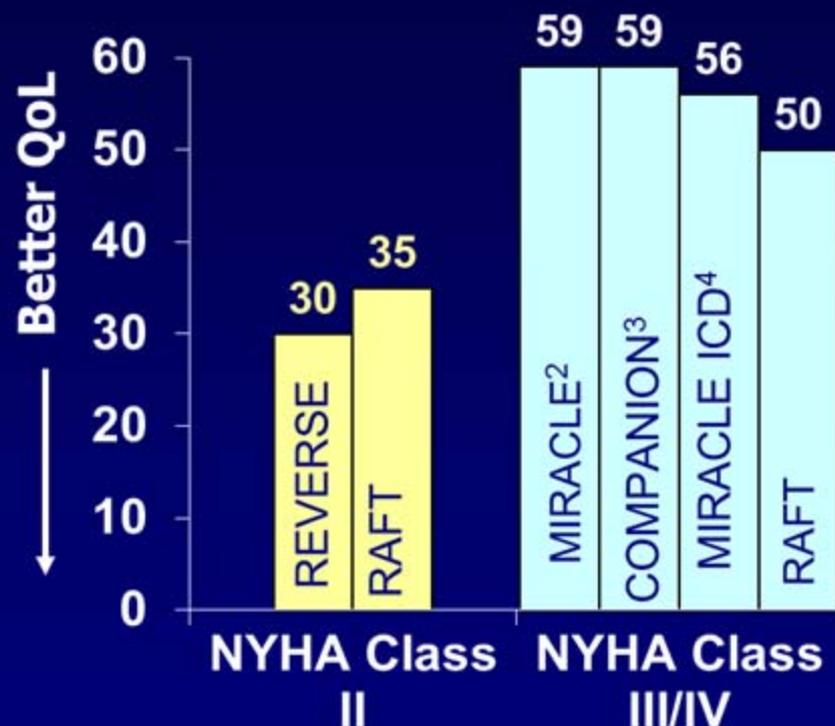
**CRT-D Better**      **ICD Better**

# REVERSE and RAFT Exercise Capacity and Quality of Life Consistent with Milder Symptoms

Baseline Mean 6 Minute Walk Distance



Baseline Mean Minnesota Living with HF Score



\* 15% of MADIT CRT = NYHA Class I

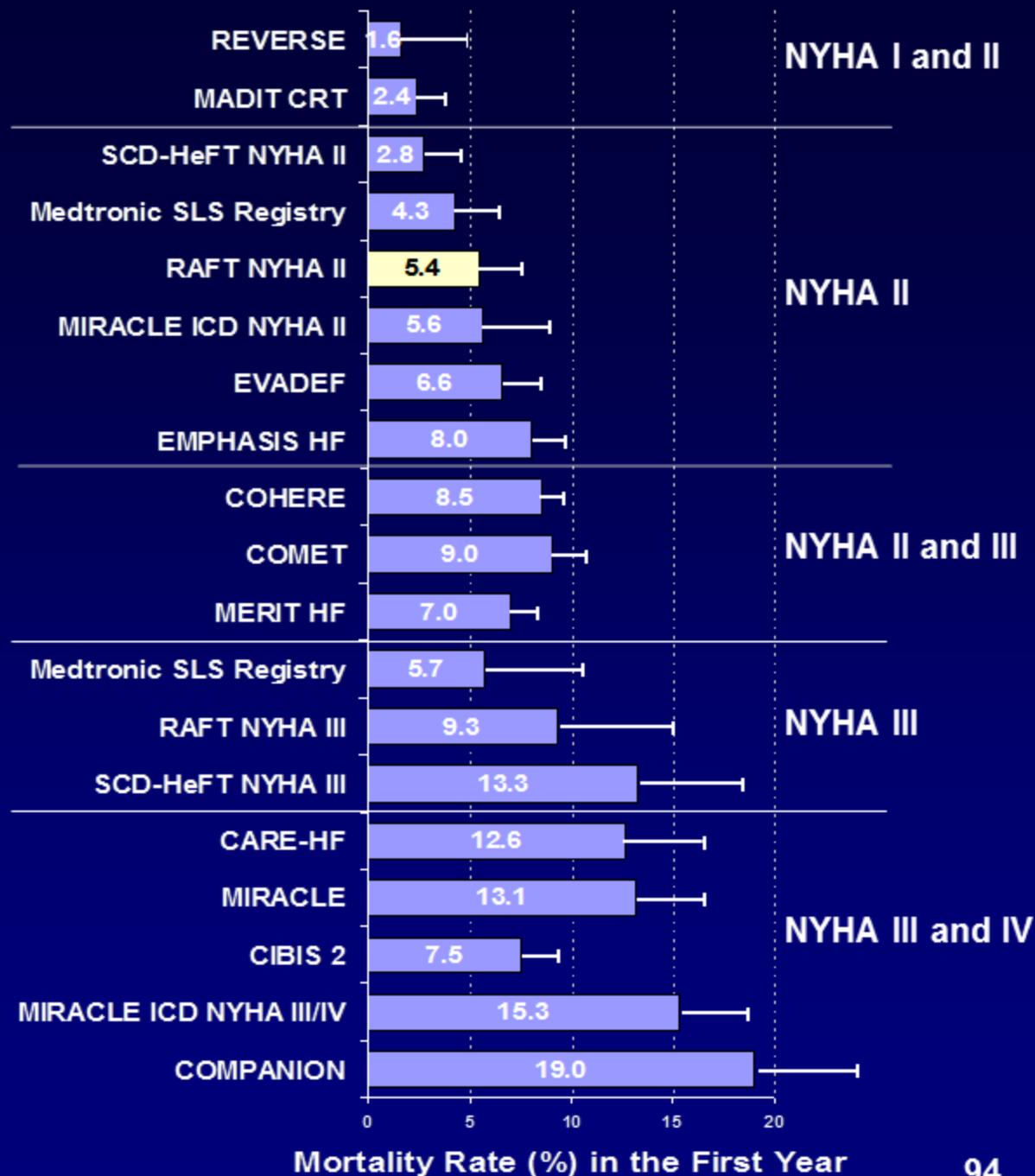
<sup>1</sup>Moss AJ, et al. N Engl J Med 2009; 361(14): 1329-38

<sup>2</sup>Medtronic (2002). InSync Cardiac Resynchronization System Final Report

<sup>3</sup>Bristow BR, et al. N Engl J Med 2004; 350: 2140-2150

<sup>4</sup>Medtronic Model 7272 InSync ICD Cardiac Resynchronization System Final Clinical Report

# Comparison of Mortality Rates Over Time Between Trials



# Revisions to RAFT Protocol

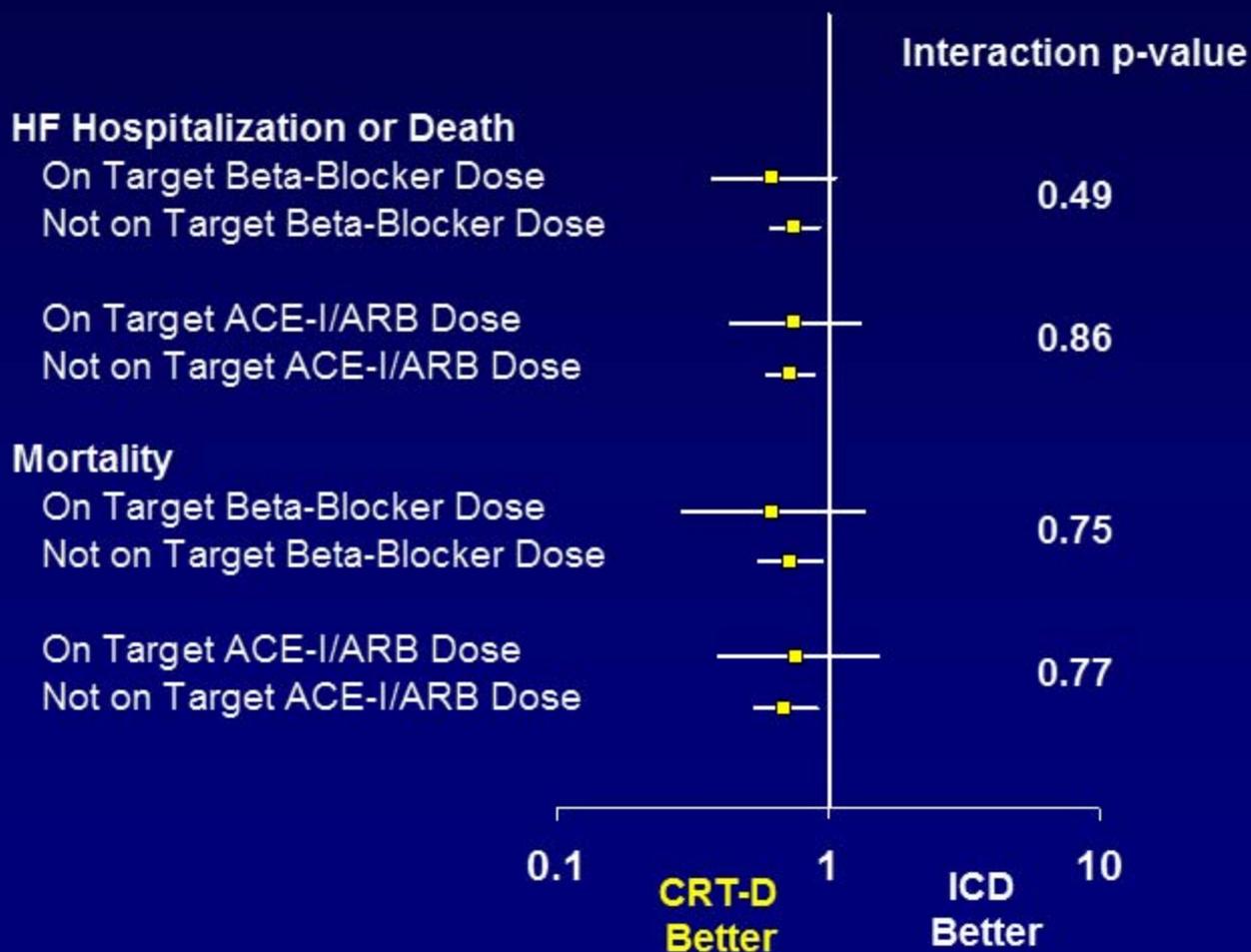
# Key RAFT Protocol Changes

- Inclusion criteria for QRS duration modified from  $\geq 130$  ms to  $\geq 120$  ms
- Enrollment of NYHA Class III patients ceased
- Number of planned interim analyses changed from three to two

# **RAFT Heart Failure Medication Optimization**

# RAFT NYHA Class II: Effect of Target Dose on Results

Hazard Ratio with 95% CI



# Post-approval Study

# Post-approval Study Proposal

- **Study Design**

- Utilize NCDR @ ICD Registry™ to confirm patient survival probability observed in REVERSE and RAFT

- **Population**

- ICD-indicated NYHA Class II patients with:
  - LVEF  $\leq$  30%,
  - QRS  $\geq$  120ms, and
  - Left bundle branch block

- **Sample size**

- 1500 patient minimum
- Provides two-sided 95% confidence interval with a width less than 5% if 5-year mortality rate is 25%.

- **Analysis time point**

- Final analysis conducted at 5 years after the last qualified study subject is identified

# Concluding Remarks

# **CRT-D' s Benefit Outweighs Risk**

- **Consistent Benefit:**
  - **Significant reduction in morbidity and mortality**
  - **Significant improvement in cardiac structure**
- **Risk:**
  - **LV lead complication rate similar to other CRT trials**

# **Medtronic Cardiac Resynchronization Therapy with Implantable Cardioverter Defibrillator (CRT-D) for Mildly Symptomatic Heart Failure**

**FDA Circulatory Systems Panel  
December 7, 2011  
Sponsor Presentation**

Backup Slides Shown

## Table 20: REVERSE Resolution of Procedure, System, or Therapy-related Complications Occurring Post-implant (excluding medical device changes)(post hoc analysis)

Table 20: REVERSE Resolution of Procedure, System, or Therapy-related Complications Occurring Post-implant (excluding medical device changes) (post-hoc analysis)

	Time from complication onset to resolution (for resolved), last AE update (for unresolved), or death					Total
	0-3 days	4-7 days	8-21 days	22-60 days	>60 days	
Resolved, no surgery	19 (7.7%)	8 (3.2%)	11 (4.5%)	4 (1.6%)	9 (3.6%)	51 (20.7%)
Resolved after surgery	65 (26.3%)	33 (13.4%)	25 (10.1%)	30 (12.2%)	30 (12.2%)	183 (74.1%)
Unresolved, no surgery	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	2 (0.8%)
Unresolved after surgery	1 (0.4%)	0 (0%)	1 (0.4%)	1 (0.4%)	2 (0.8%)	5 (2.0%)
Death <sup>x</sup>	4 (1.6%)	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	6 (2.4%)
<b>Total</b>	<b>90 (36.4%)</b>	<b>43 (17.4%)</b>	<b>37 (15.0%)</b>	<b>35 (14.2%)</b>	<b>42 (17.0%)</b>	<b>247</b>

x Two were conservatively classified as procedure-related due to the death occurring within 30 days post-implant; 4 were sudden deaths with scant information available. All 4 patients had a CRT-D device. Since there was no device interrogation data to rule out the possibility that a ventricular arrhythmia occurred that the CRT-D did not appropriately treat, the AEAC conservatively classified them as related to the system.

# REVERSE Crossover Definition

- **Definition of crossover:**

**CRT OFF**  
**Pacing Mode was DDD  
or DDDR**  
**Ventricular Pacing  
was RV+LV**

**CRT ON**  
**Pacing Mode was not  
DDD or DDDR**  
**Ventricular Pacing  
was not RV+LV**

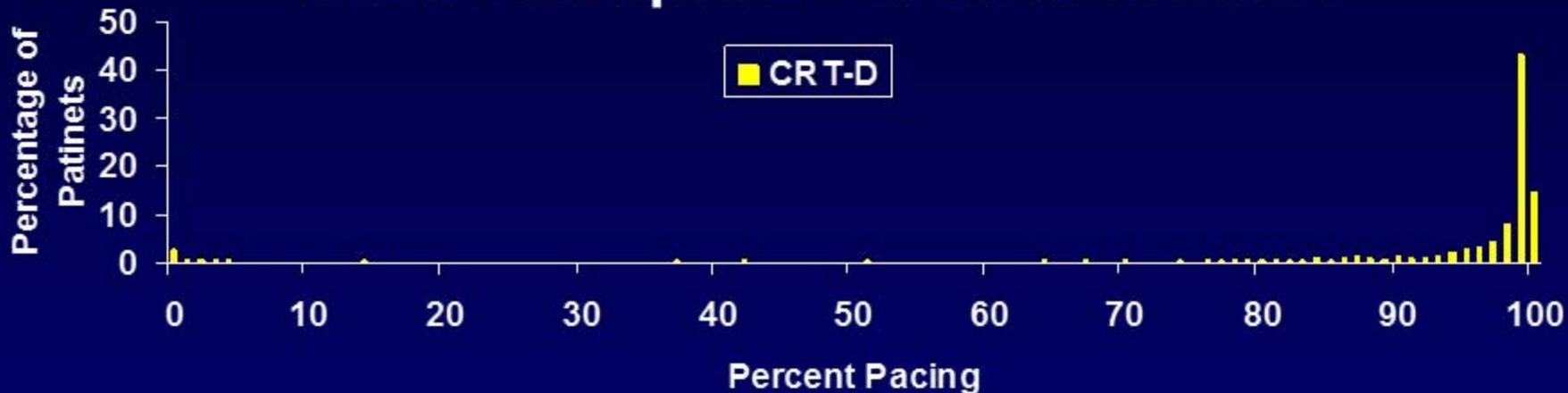
- **Crossover due to worsening heart failure was a subset of all crossovers**
- **Confirmed by: crossover CRF, save-to-disk data, center reports**
- **Permanent crossover defined as not corrected prior to end of randomization**
- **Temporary crossover defined as corrected prior to end of randomization**

## Percent Pacing at 12 Months in Patients Randomized to CRT OFF in REVERSE

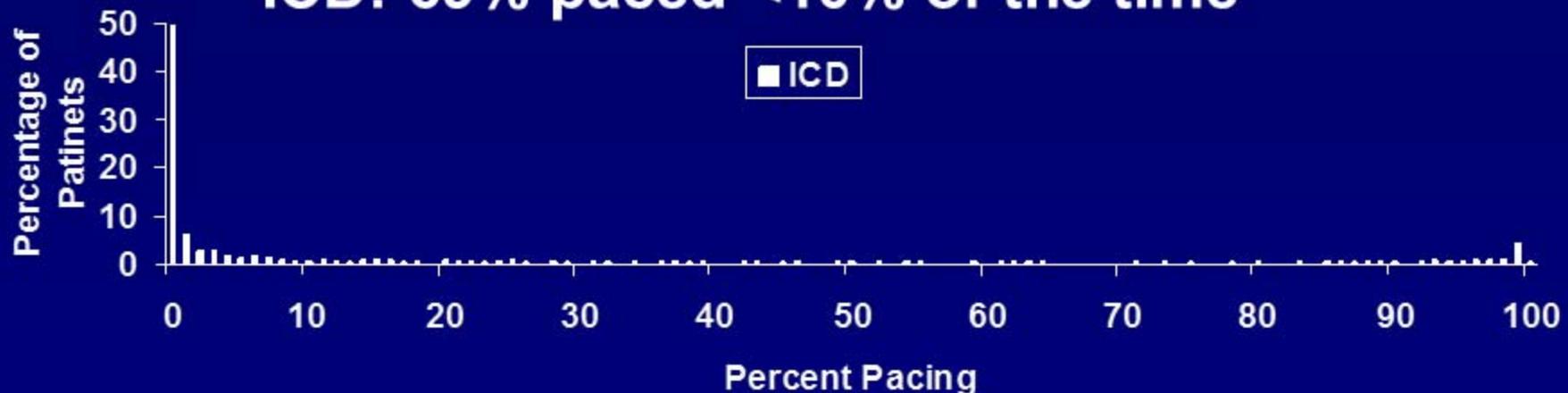
<b>% Pacing</b>	<b>CRT OFF (n=191)</b>
<b>0%</b>	<b>81% (155)</b>
<b>&lt;1%</b>	<b>6% (11)</b>
<b>1-10%</b>	<b>3% (5)</b>
<b>10-50%</b>	<b>6% (11)</b>
<b>50-80%</b>	<b>2% (4)</b>
<b>80-90%</b>	<b>2% (3)</b>
<b>90-95%</b>	<b>1% (1)</b>
<b>95-98%</b>	<b>0% (0)</b>
<b>98-99%</b>	<b>1% (1)</b>
<b>100%</b>	<b>0% (0)</b>

# RAFT Percent Pacing

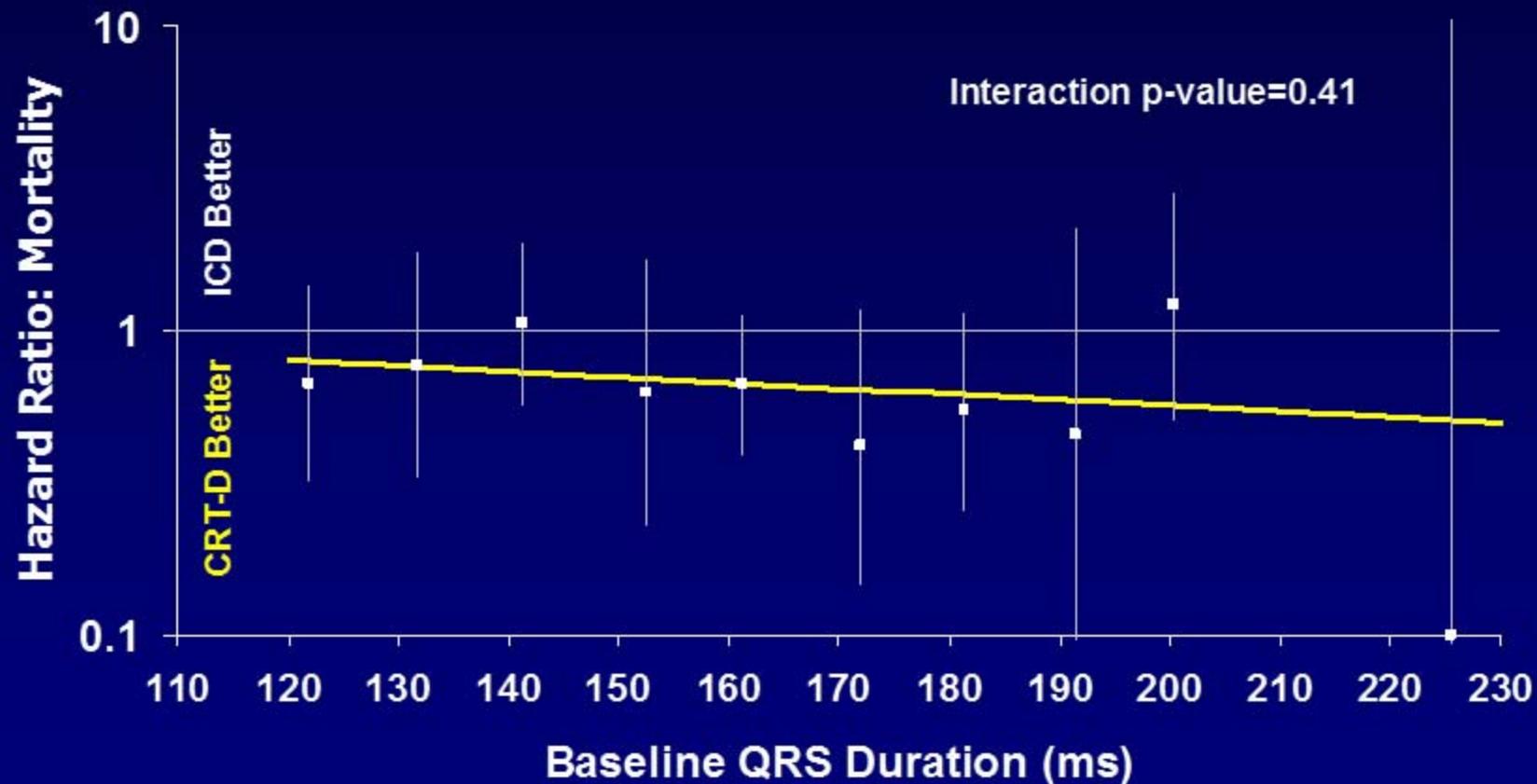
**CRT-D: 82% paced >90% of the time**



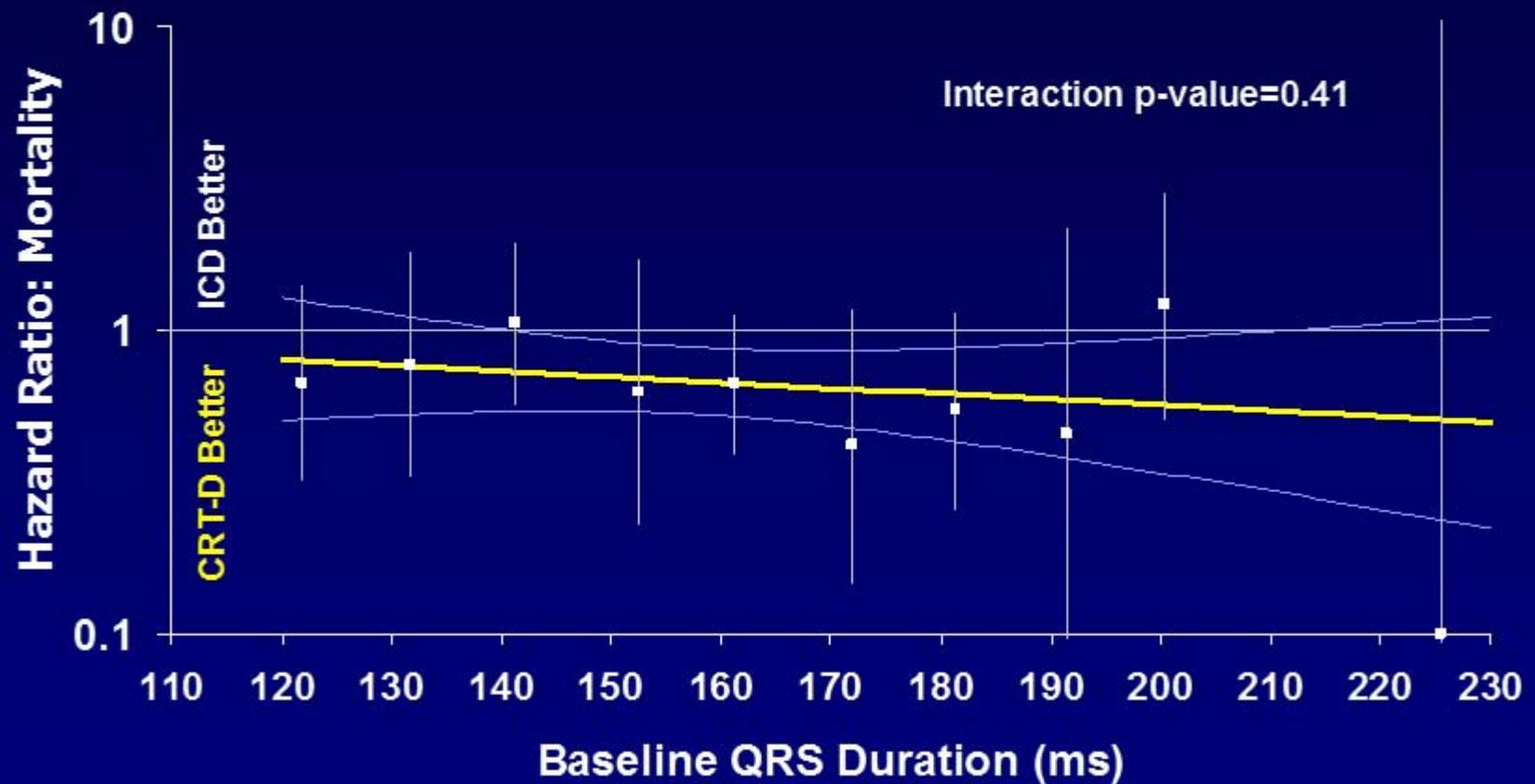
**ICD: 69% paced <10% of the time**



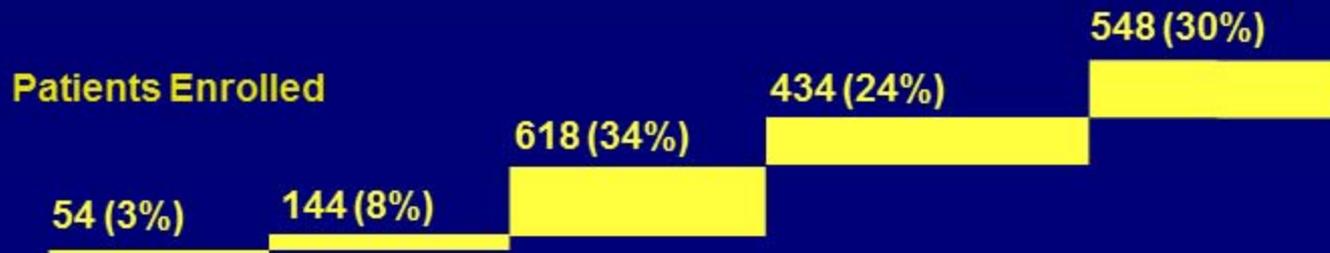
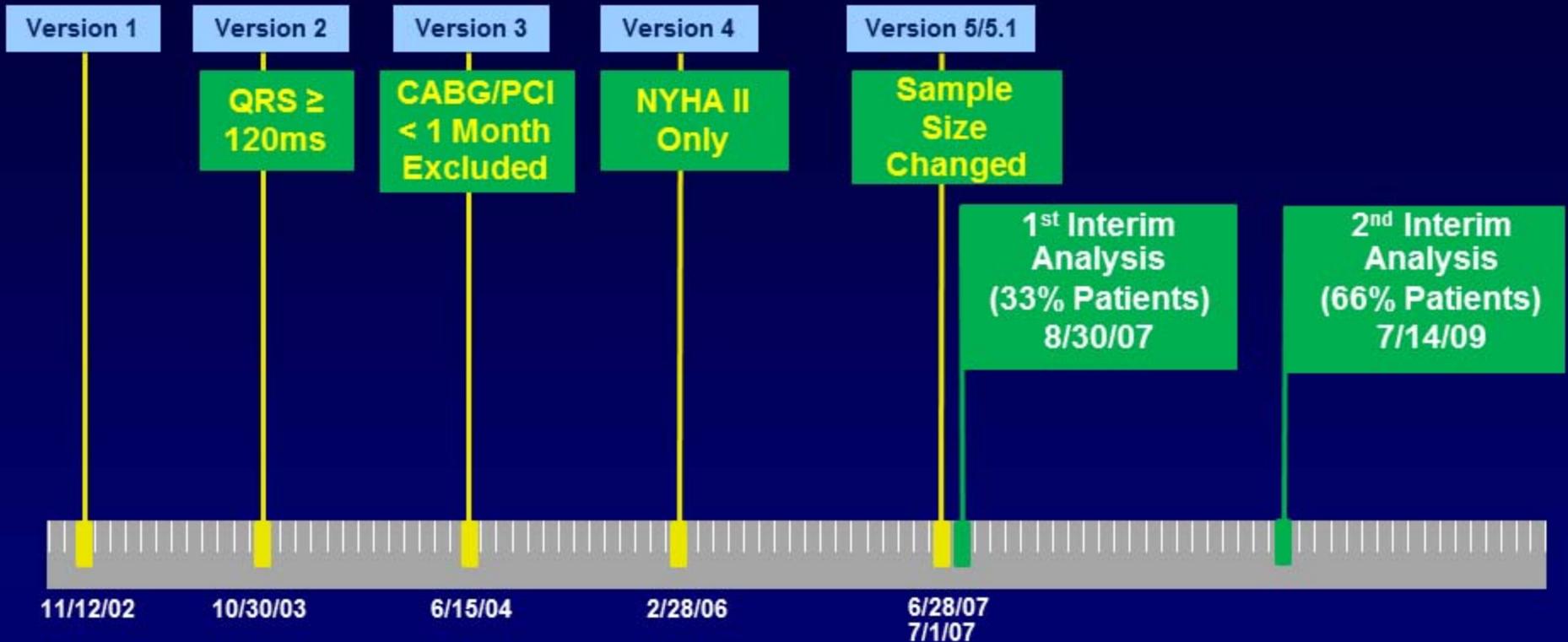
# RAFT NYHA Class II: Mortality



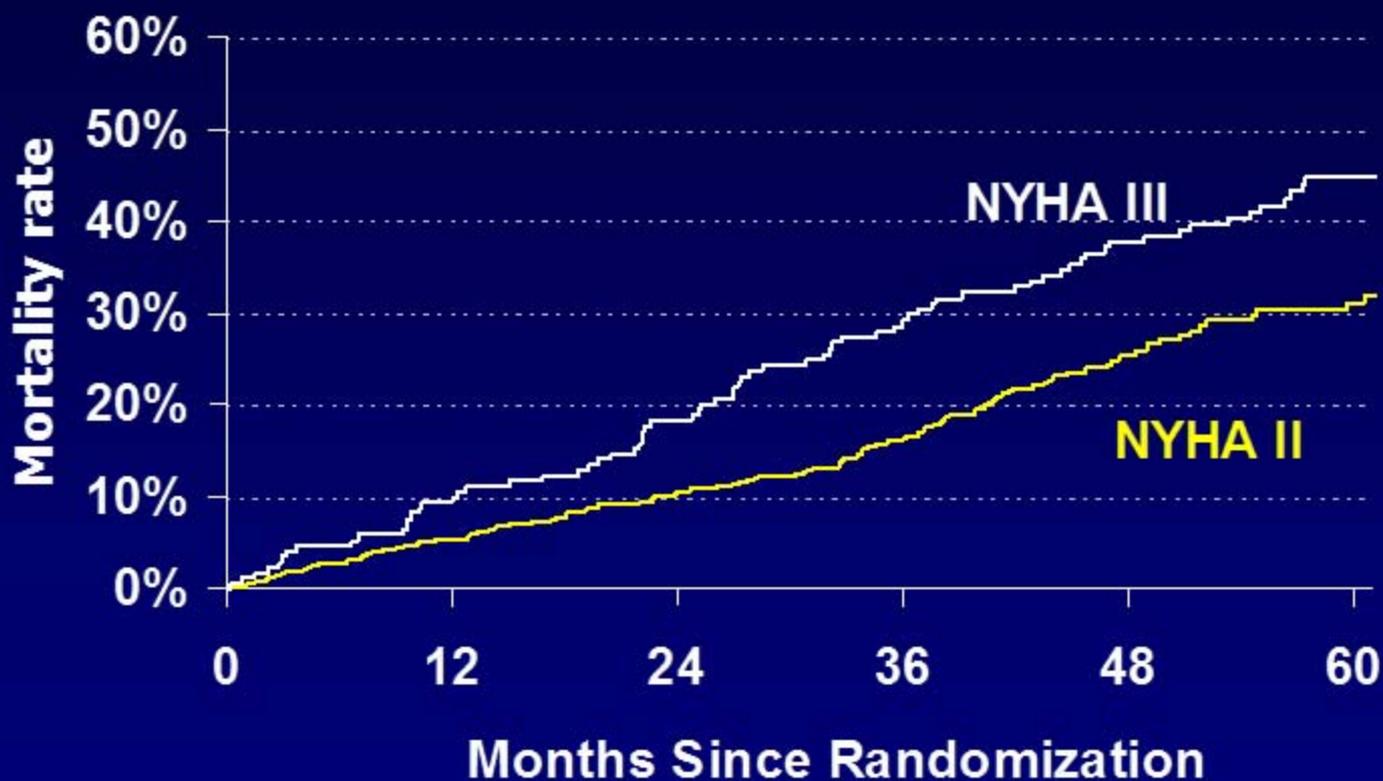
# RAFT NYHA Class II: Mortality



# RAFT Timeline



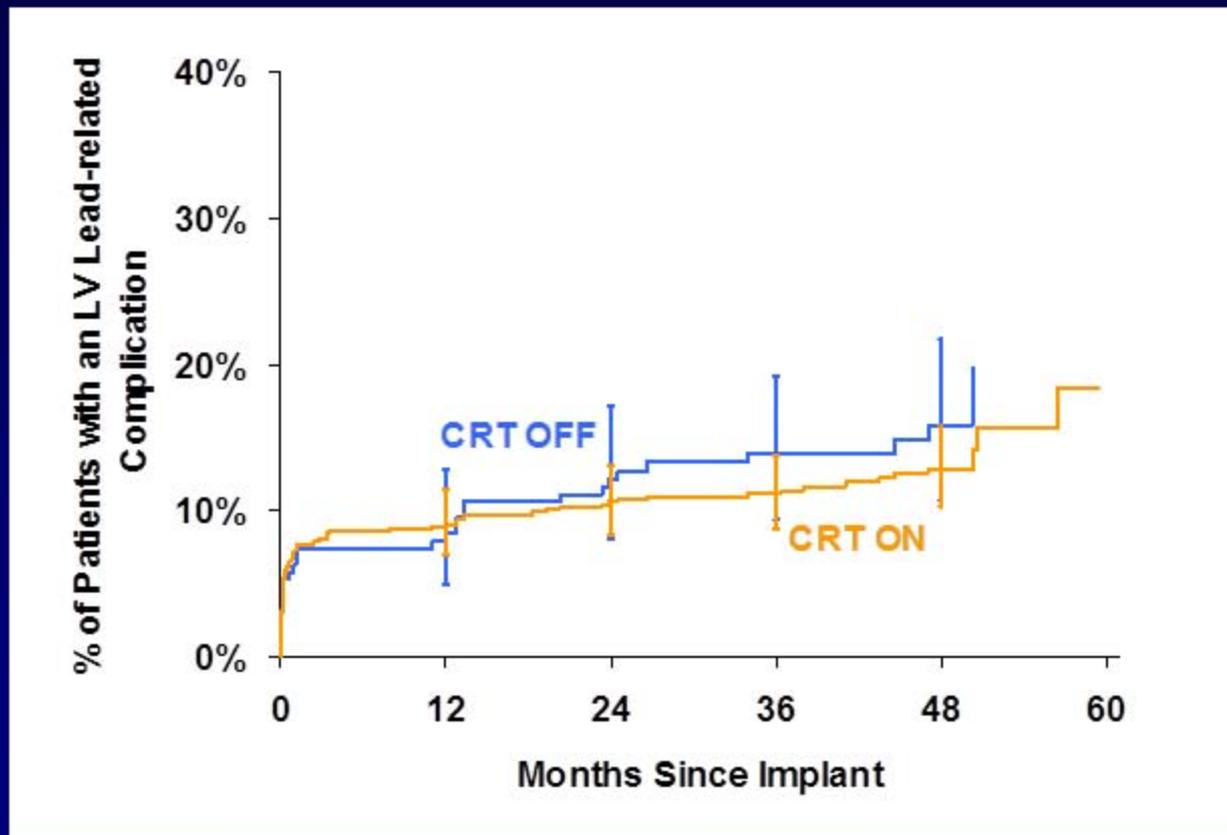
# All-cause Mortality Rate In RAFT ICD Cohort: NYHA Class II vs. Class III



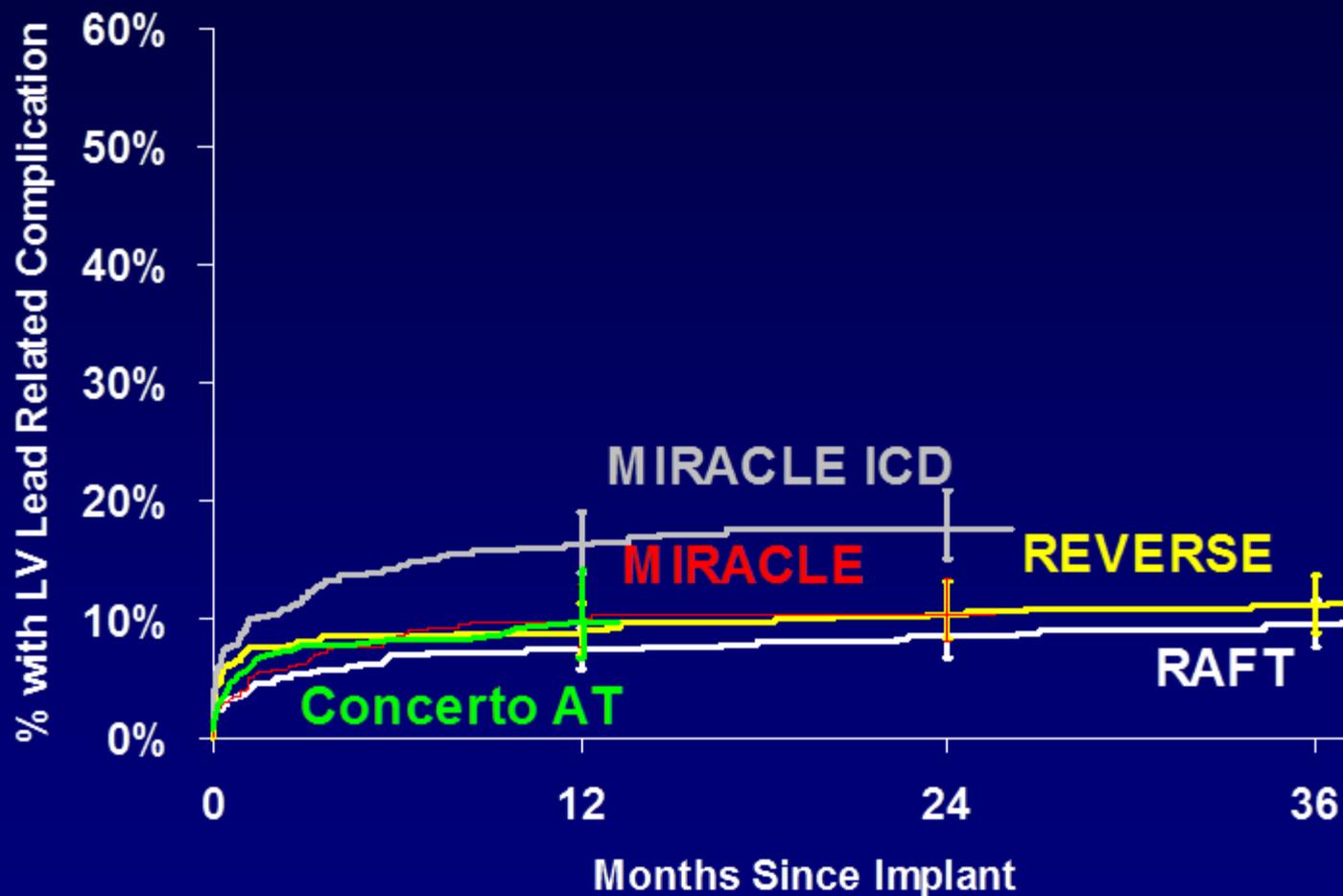
Number	730	687	533	366	189	83
remaining	174	154	137	116	100	66

# LV Lead-related Complications Similar between Groups in REVERSE

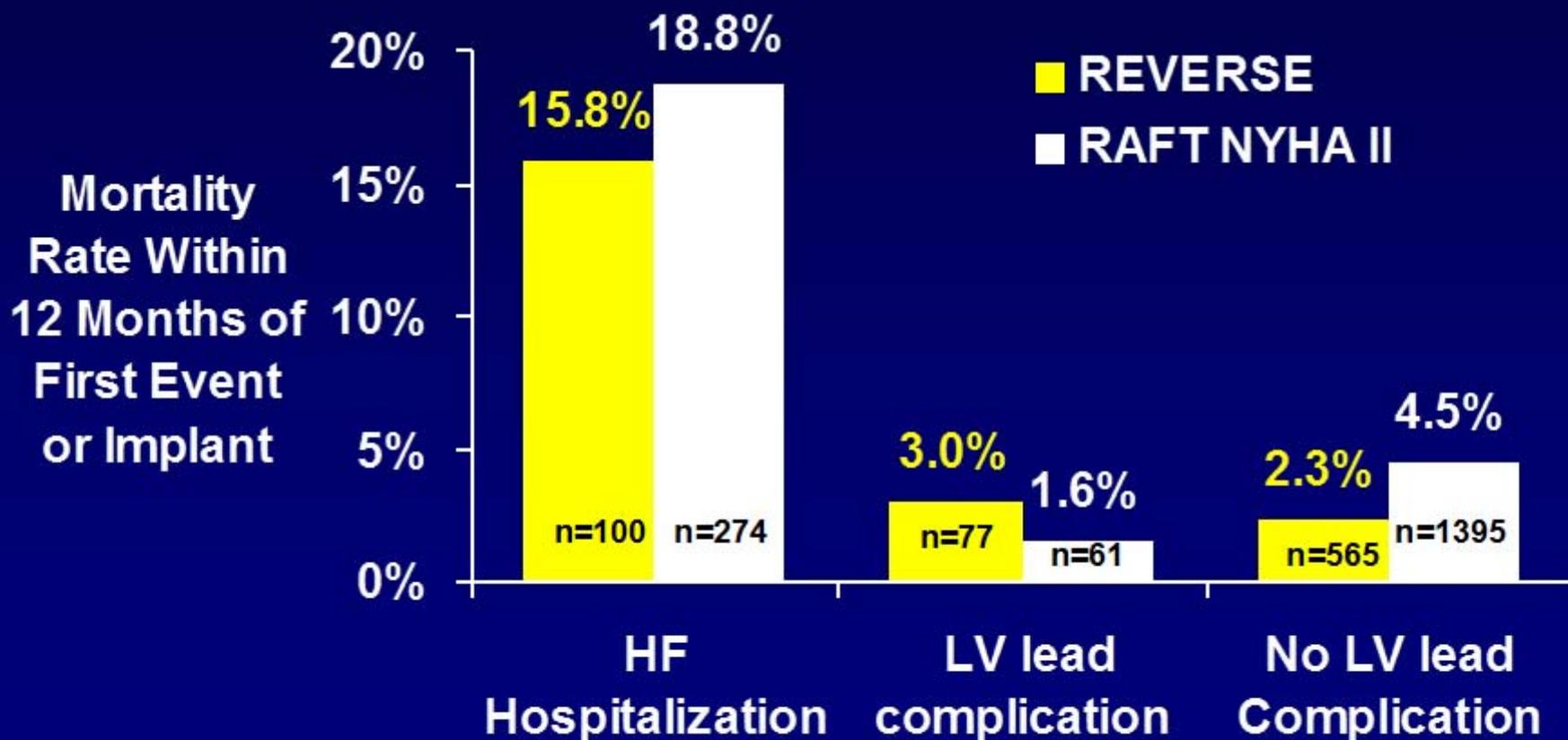
## Time to First LV Lead-related Complication



# LV Lead-related Complication Rates in REVERSE and RAFT Similar to Rates Observed in Studies of NYHA III/IV Patients



# REVERSE and RAFT: Mortality Within 12 Months of First HF Hospitalization or LV Lead Complication

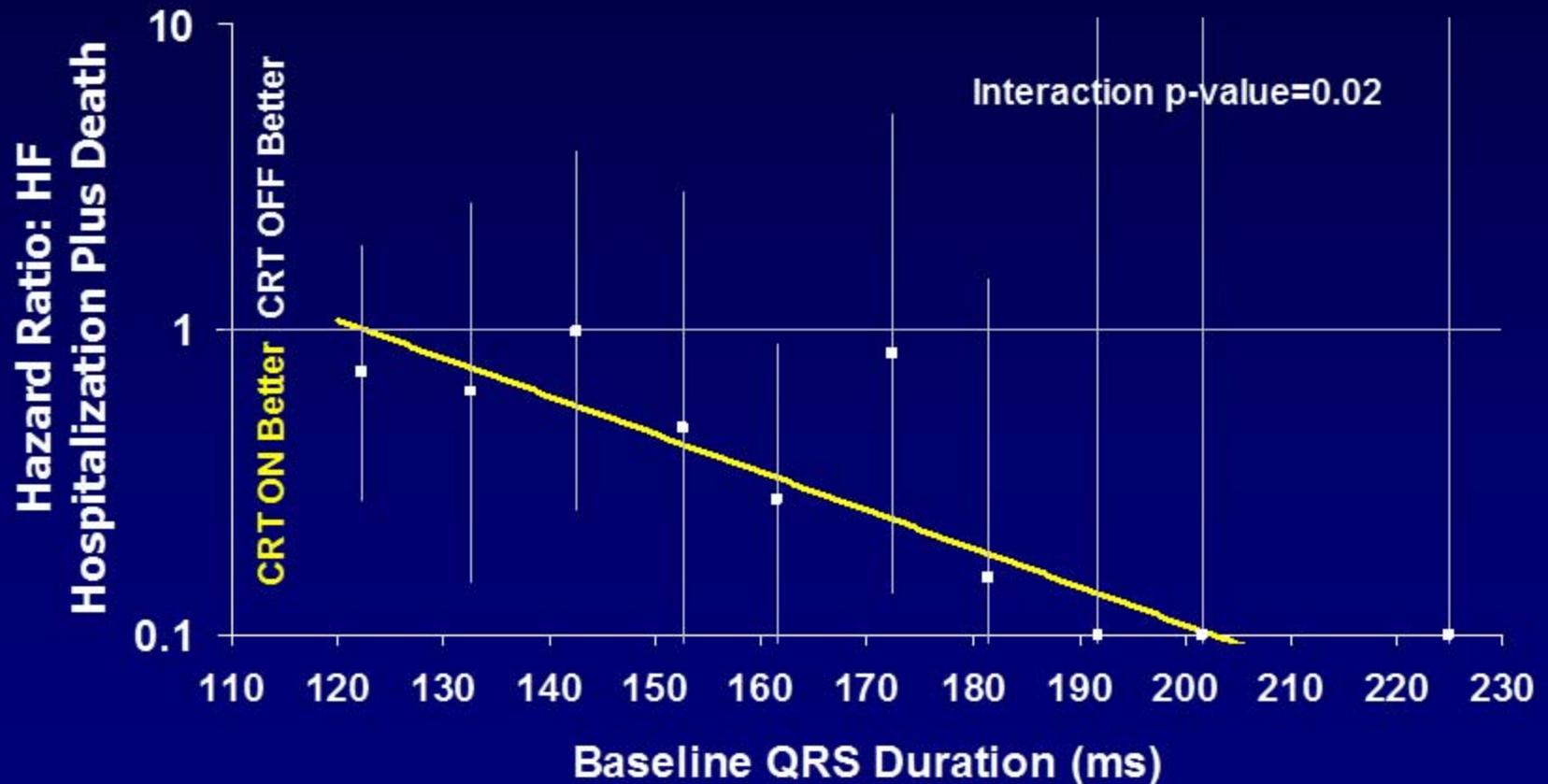


## Table 29: Baseline Characteristics of Proposed Patient Population: REVERSE and RAFT

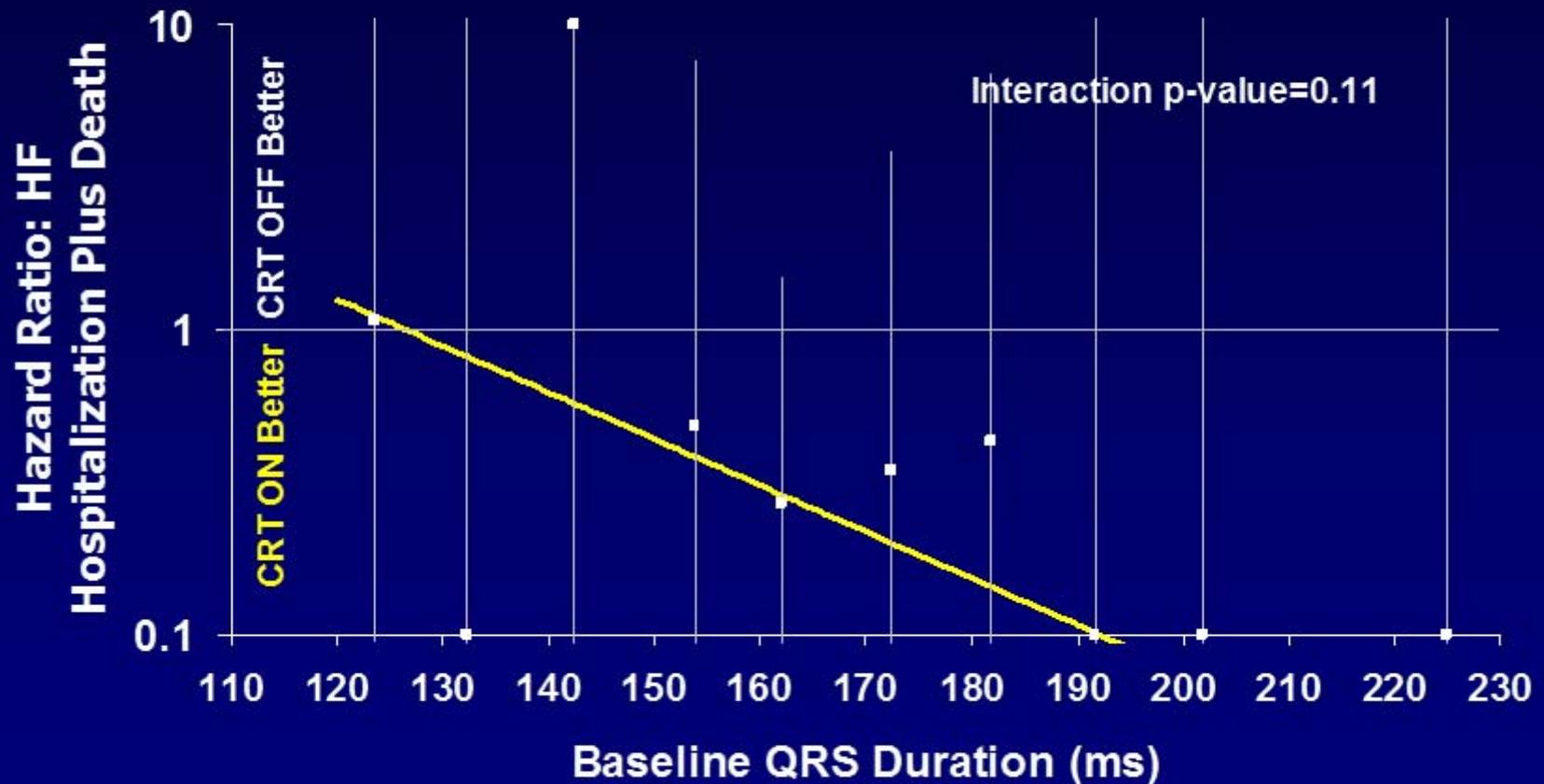
Table 29: Baseline Characteristics of Proposed Patient Population: REVERSE and RAFT

	REVERSE (n=189)	RAFT (n=947)
Age (yrs)	61.9 ± 12.0	65.0 ± 9.3
Male	75%	82%
Ischemic	41%	61%
LVEF (%)	22.8 ± 5.3	22.5 ± 5.2
Minnesota Living with HF Score	29.3 ± 20.0	34.6 ± 21.3
6-minute Hall Walk (m)	400 ± 117	373 ± 105
QRS Duration (ms)	164 ± 21	161 ± 25
On ACE-I/ARBs	97%	97%
On beta blocker	95%	91%
On diuretics	80%	81%
On lipid-lowering agent	58%	75%
On Digitalis/cardiac glycosides	31%	30%
Coronary artery disease	41%	51%
Myocardial infarction	34%	53%
Hypertension	49%	46%
Previous CABG	19%	30%
Diabetes	22%	32%
Serum Creatinine (mg/dL)	1.1 ± 0.3	1.2 ± 0.7
eGFR (mL/min/1.73m <sup>2</sup> )	73.6 ± 24.8	63.4 ± 21.1
Systolic Blood Pressure (mmHg)	124.6 ± 18.3	118.5 ± 17.1
Diastolic Blood Pressure (mmHg)	71.8 ± 11.5	68.7 ± 10.2

# REVERSE Full Cohort: HF Hospitalization or Death



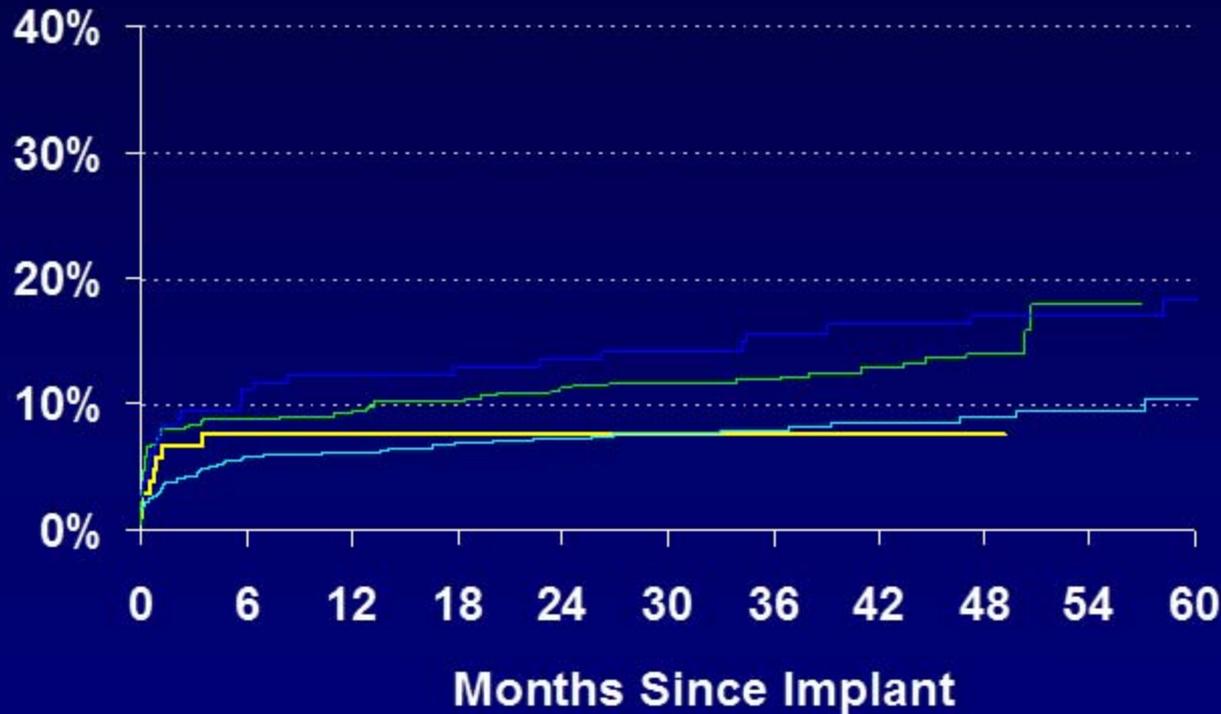
# REVERSE Proposed Population: HF Hospitalization or Death



# Heart-failure Hospitalization or All-cause Death: Proposed Patient Population QRS < 150 ms

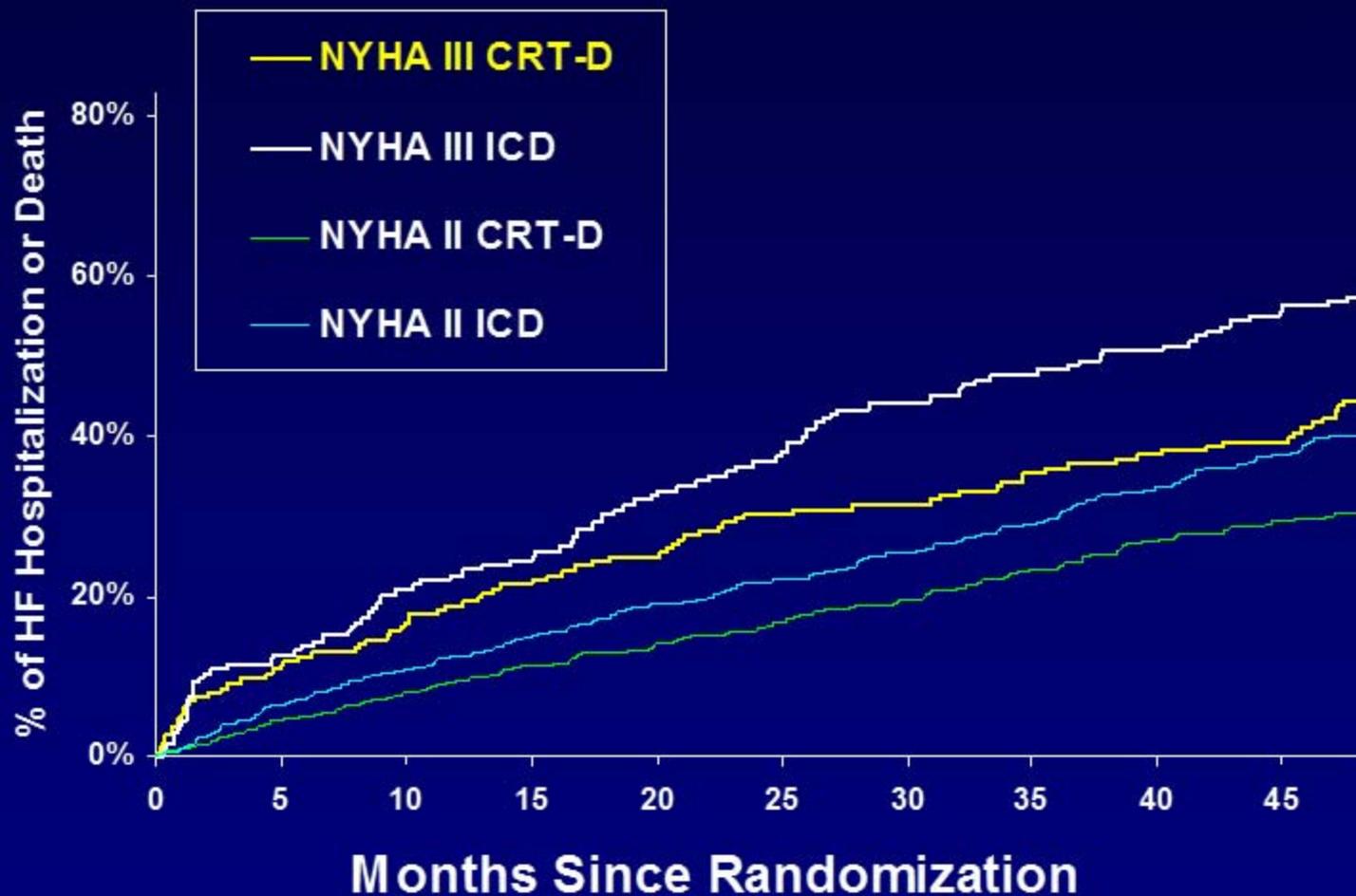
	<b>N</b>	<b>HR</b>	<b>95% CI</b>
<b>REVERSE</b>	<b>42</b>	<b>0.51</b>	<b>(0.1, 2.9)</b>
<b>RAFT</b>	<b>298</b>	<b>0.89</b>	<b>(0.6, 1.3)</b>

# LV Complications

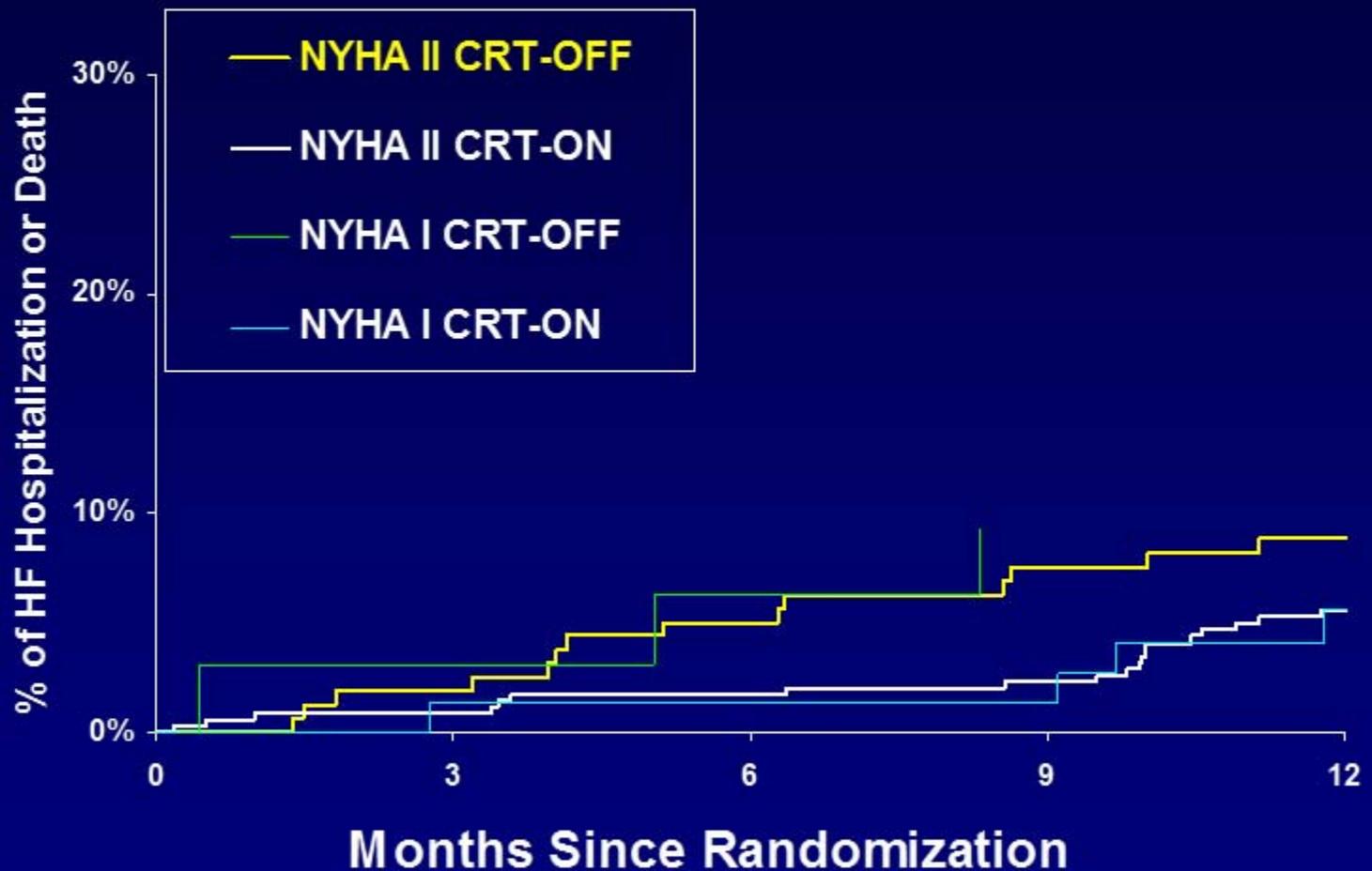


**RAFT NYHA III**  
(n=358)  
**RAFT NYHA II**  
(n=1429)  
**REVERSE NYHA II**  
(n=514)  
**REVERSE NYHA I**  
(n=107)

# RAFT: HF Hospitalization and All-cause Mortality Rate



# REVERSE: HF Hospitalization and All-cause Mortality Rate



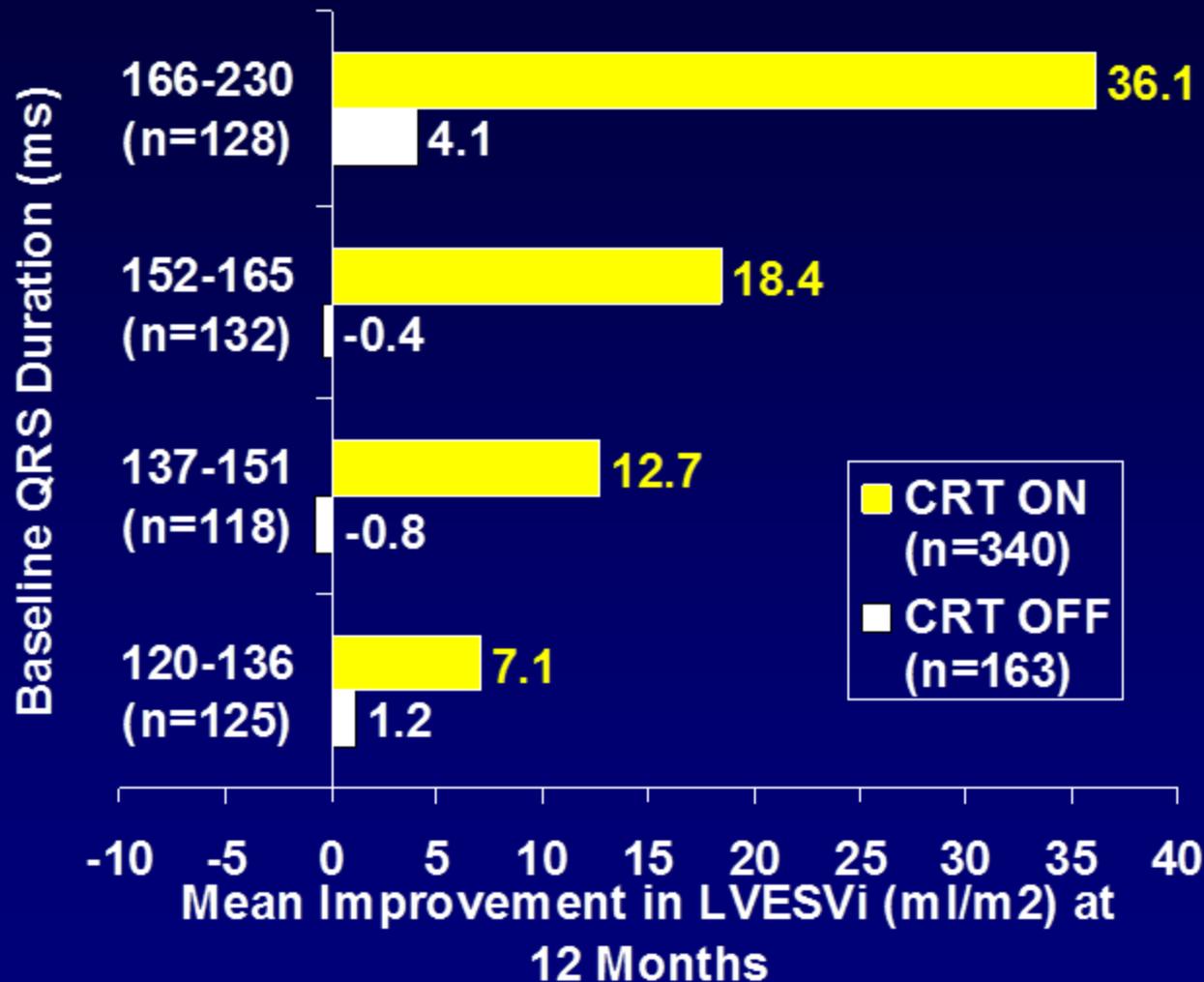
# RAFT PPP: Balanced Distribution of Baseline Characteristics

Patient Characteristics	CRT-D (N=477)	ICD (N=470)	p-value
Age	65.0 ± 9.5	65.0 ± 9.1	0.9790
Male	79(17%)	95(20%)	0.1543
Ischemic	304(64%)	274(58%)	0.0957
LVEDF	22.4 ± 5.3	22.6 ± 5.1	0.5607
QRS	159.6 ± 24.6	162.3 ± 24.6	0.0948
ACE-I/ARBs	457(96%)	457(97%)	0.2881
Beta-blockers	440(92%)	421(90%)	0.1748
Myocardial infarction	267(56%)	233(50%)	0.0547
Hypertension	225(47%)	206(44%)	0.3277
Diabetic	147(31%)	154(33%)	0.5306
Creatinine (mg/dL)	1.2 ± 0.6	1.2 ± 0.7	0.9073
GFR	62.5 ± 19.4	64.3 ± 22.7	0.1859
Supine systolic blood pressure (mmHg)	118.6 ± 17.3	118.4 ± 17.0	0.8562
Supine diastolic blood pressure (mmHg)	68.5 ± 10.3	68.8 ± 10.0	0.6443

# REVERSE PPP: Balanced Distribution of Baseline Characteristics

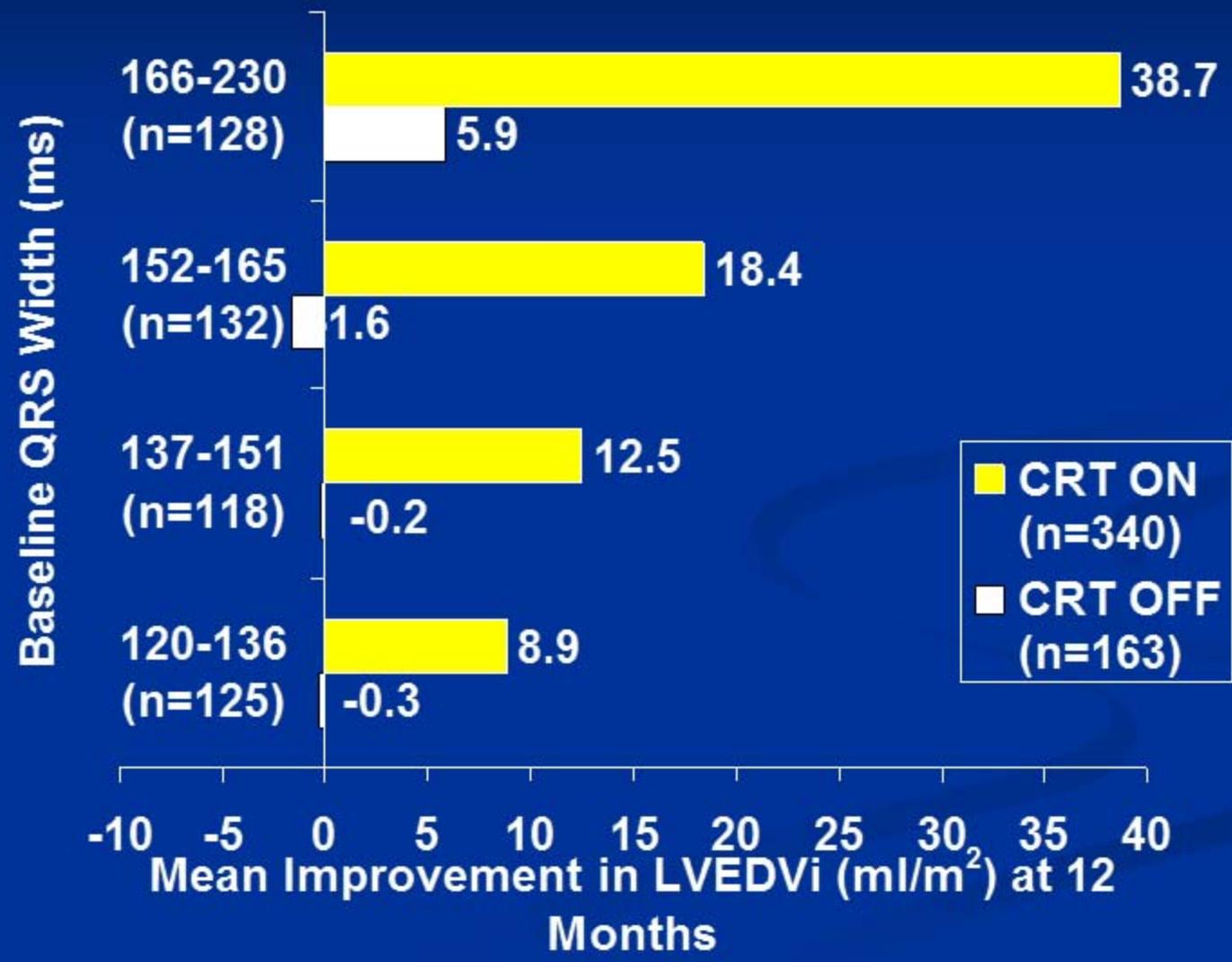
Patient Characteristics	OFF (N=64)	ON (N=125)	p-value
Age at enrollment (years)	59.3 ± 12.6	63.2 ± 11.6	0.0371
Male	46(72%)	95(76%)	0.5973
Ischemic	22(34%)	56(45%)	0.2118
LVEF	22.9 ± 5.5	22.7 ± 5.2	0.8265
QRS	165.7 ± 21.0	162.8 ± 20.5	0.3626
ACE-I/ARBs	62(97%)	122(98%)	1.0000
Beta-blockers	59(92%)	121(97%)	0.1694
Myocardial infarction	19(30%)	46(37%)	0.4187
Hypertension	31(48%)	61(49%)	1.0000
Diabetes	19(30%)	22(18%)	0.0640
Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3	0.8212
GFR	76.9 ± 27.8	71.8 ± 23.1	0.1847
Supine systolic blood pressure (mmHg)	123.8 ± 18.4	125.0 ± 18.3	0.6682
Supine diastolic blood pressure (mmHg)	71.5 ± 12.9	71.9 ± 10.8	0.8548

# REVERSE: LVESVi Improvement by QRS Duration in Quartiles

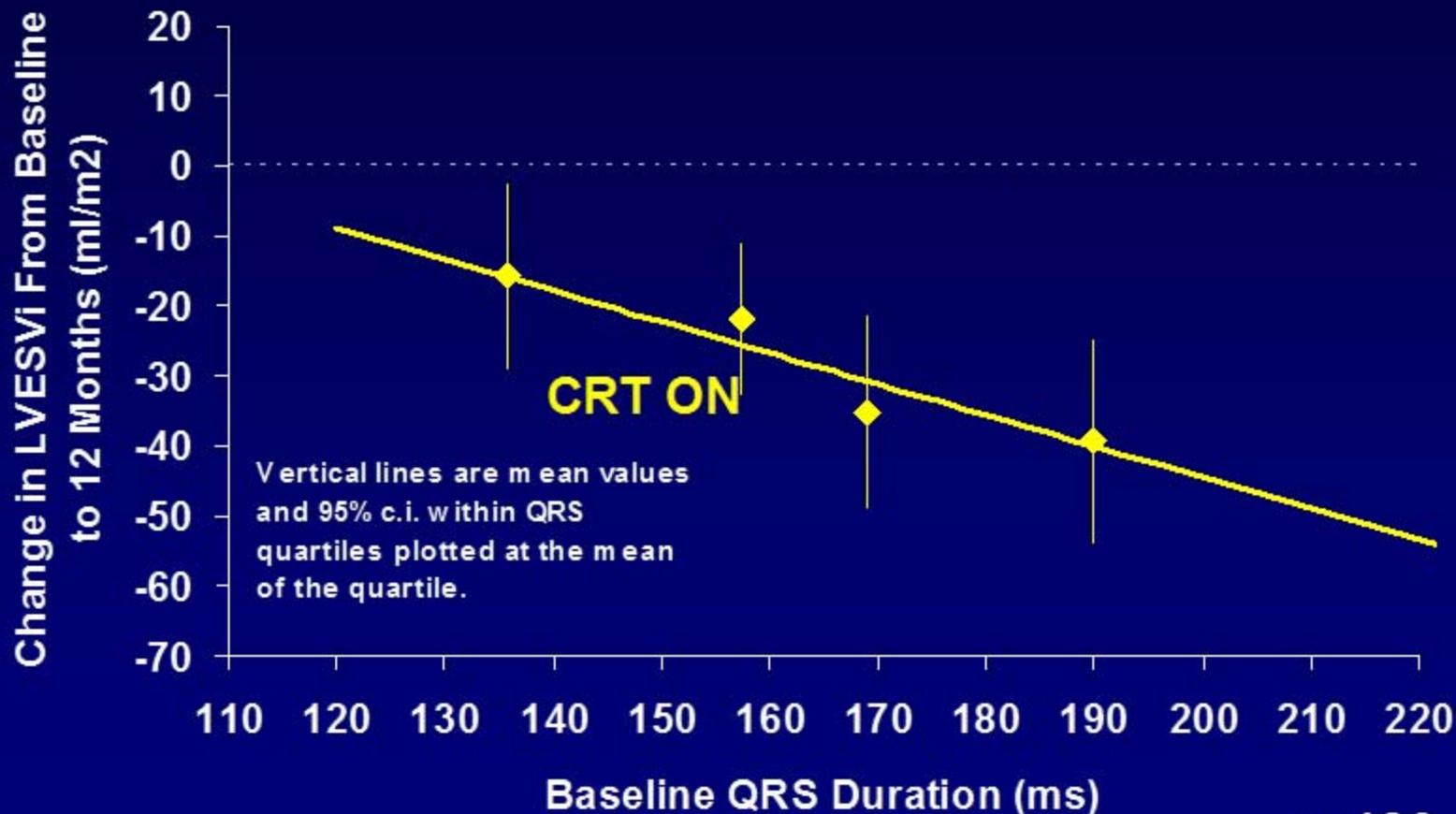


\* Gold MR, et al. Presented at AHA, 2009.

# Change in LVEDVi by QRS Width



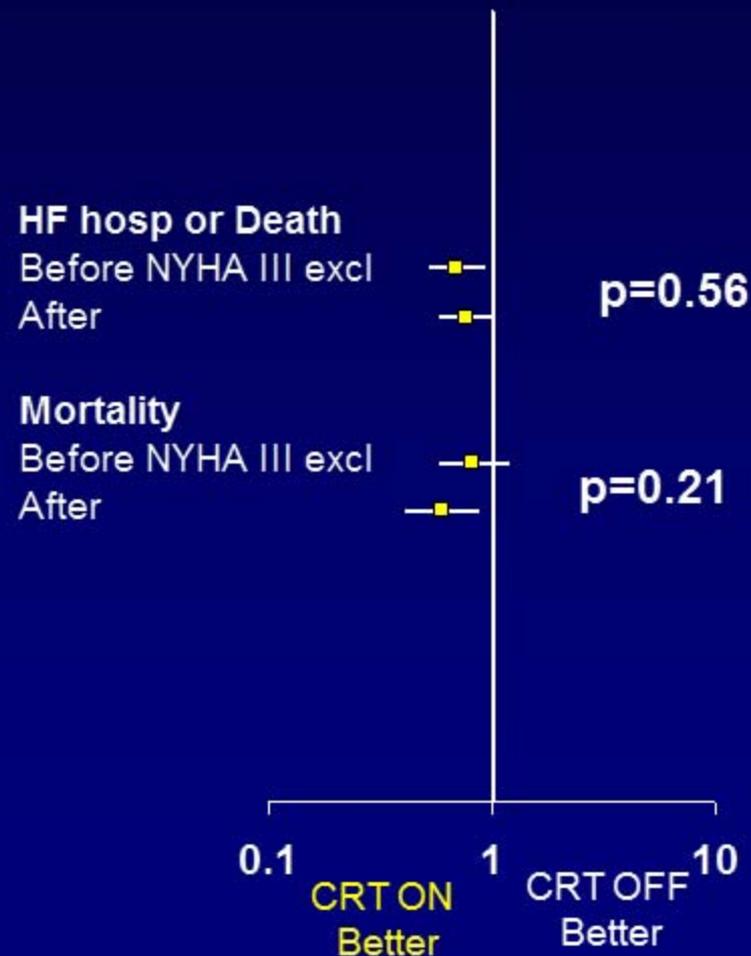
# REVERSE: CRT Beneficial Across QRS Durations for LVESVi in the Proposed Population



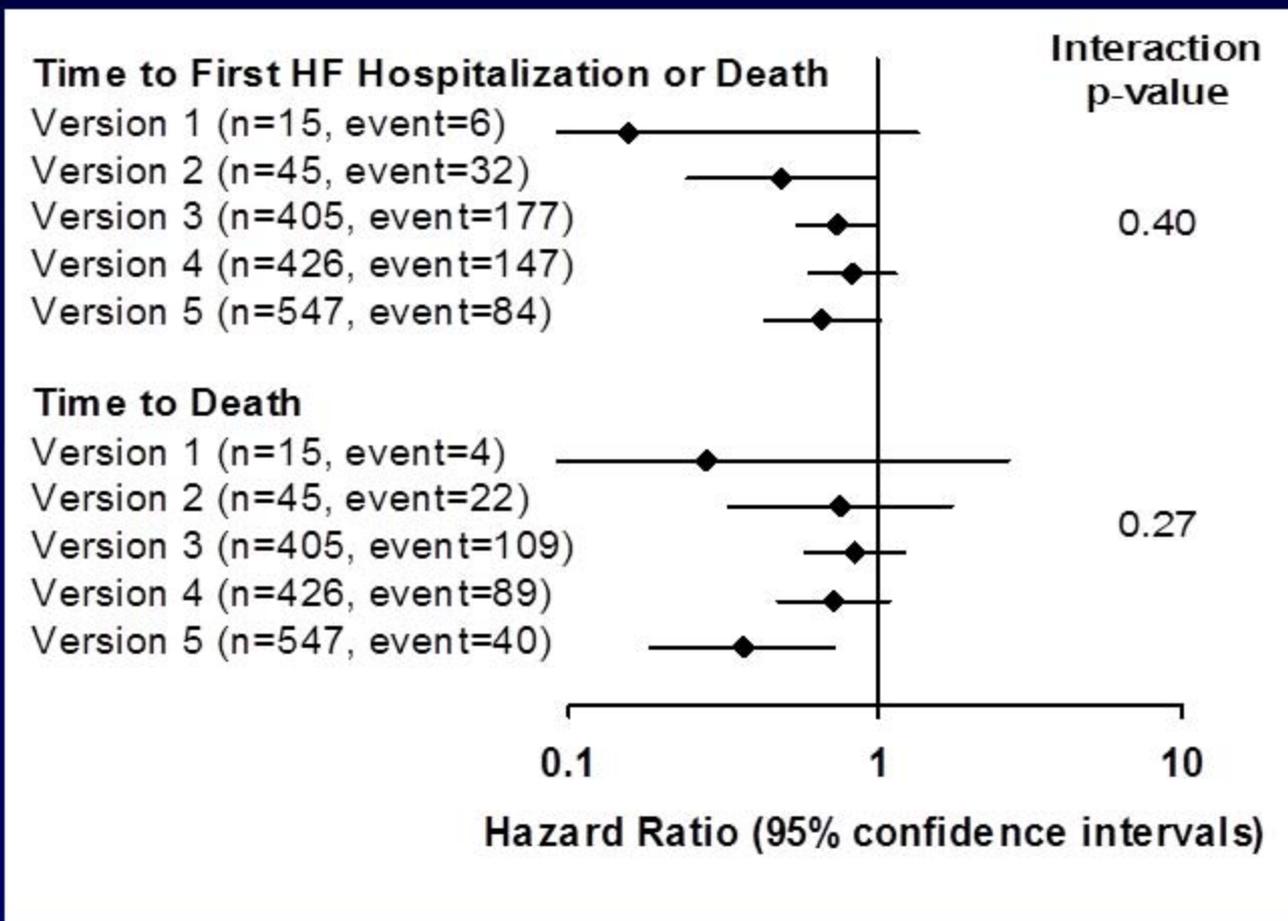
n=189

# RAFT NYHA II: Primary and Secondary Endpoint Before and After NYHA III Excluded

Hazard Ratio with 95% CI



# RAFT NYHA Class II: Primary and Secondary Endpoint Results by Protocol Version



## REVERSE and RAFT Patients were on Optimal Medical Therapy at Enrollment - Beta Blockers

Study	n	Percent on Beta Blocker	Mean Beta Blocker Dose (mg/day) 50 mg Carvedilol equivalent	Percent at Target Dose (50 mg Carvedilol equivalent)
REVERSE	610	95%	26.1 ± 18.1	25%
RAFT NYHA Class II	1438	89%	25.2 ± 17.3	18%
MADIT-CRT <sup>1</sup>	1820	93%	28 ± 19	27%
IMPROVE HF <sup>2</sup>	6109	89%	Not reported	21%*
SHIFT <sup>3</sup> Patients on Carvedilol only	2604	89%	25.0 ± 17.8	26%

\* % based on patients eligible for beta blocker therapy, not entire cohort

<sup>1</sup> FDA Circulatory Systems Panel Meeting: MADIT-CRT panel materials, 18 March 2010.

<sup>2</sup> Gheorghiu, M et al. Medication dosing in outpatients with heart failure after implementation of practice-based performance improvement intervention: findings from IMPROVE HF. Submitted and accepted for publication.

<sup>3</sup> Swedberg K et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010; 376: 875-885.

## REVERSE and RAFT Patients were on Optimal Medical Therapy at Enrollment - ACE-I/ARB

Study	n	Percent on ACE-I/ARB	Mean ACE-I/ARB (mg/day) (Lisinopril and Losartan equivalents)	Percent at Target Dose (20 mg Lisinopril equivalent)
REVERSE	610	96%	16.2 +/- 10.7 51.4 +/- 27.0	51%
RAFT NYHA Class II	1438	97%	16.9 +/- 9.6 50.8 +/- 36.0	58%
MADIT-CRT <sup>1</sup>	1820	96%	23 ± 17 75.9 +/- 59.1	51%
IMPROVE HF <sup>2</sup>	5919	83%	Not reported	36%*

\* % based on patients eligible for ACE-I/ARB therapy, not entire cohort

<sup>1</sup> FDA Circulatory Systems Panel Meeting: MADIT-CRT panel materials, 18 March 2010.

<sup>2</sup> Gheorghide, M et al. Medication dosing in outpatients with heart failure after implementation of practice-based performance improvement intervention: findings from IMPROVE HF. Submitted and accepted for publication. **07-19**

## REVERSE Showed No Significant Outcome Differences between US and OUS

Outcome (12 months)	Entire Cohort Interaction p-value	Proposed Population Interaction p-value
Clinical Composite Response (unadjusted)	0.11	0.50
Clinical Composite Response (adjusted)	0.16	Not adjusted
Change in LVESVi	0.38	0.93
Time to First HF Hospitalization or Death	0.26	0.87

- Difference in interaction p-value between entire and proposed cohorts driven by QRS morphology
  - Larger percentage of non-LBBB subjects in the U.S.

## Table 58: REVERSE U.S./OUS Data Pooling Logistic Regression Full Model: CCR Worsened

Table 58: REVERSE U.S./OUS Data Pooling Logistic Regression Full Model: CCR Worsened

Parameter	Level	Level	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept			1	0.4782	1.6127	0.0879	0.7668
RAND	OFF		1	-0.2476	0.1218	4.1302	0.0421
OUS	OUS		1	-0.0593	0.1331	0.1988	0.6557
AGE			1	0.000198	0.0153	0.0002	0.9897
GENDER	Male		1	-0.1190	0.1635	0.5304	0.4664
ISCHEMIC	No		1	0.000798	0.1411	0.0000	0.9955
HYPERTENSION	No		1	0.1409	0.1232	1.3071	0.2529
BMI			1	-0.0375	0.0271	1.9075	0.1672
GFR			1	0.00813	0.00583	1.9486	0.1627
LVEF			1	0.0152	0.0163	0.8672	0.3517
QRS DURATION			1	0.00287	0.00632	0.2065	0.6495
QRS MORPH	IVCD		1	0.0268	0.1959	0.0187	0.8913
QRS MORPH	LBBB		1	0.5363	0.1861	8.3041	0.0040
NYHA	I		1	-0.7718	0.1295	35.5114	<.0001
RAND*OUS	OFF	OUS	1	0.1701	0.1215	1.9601	0.1615

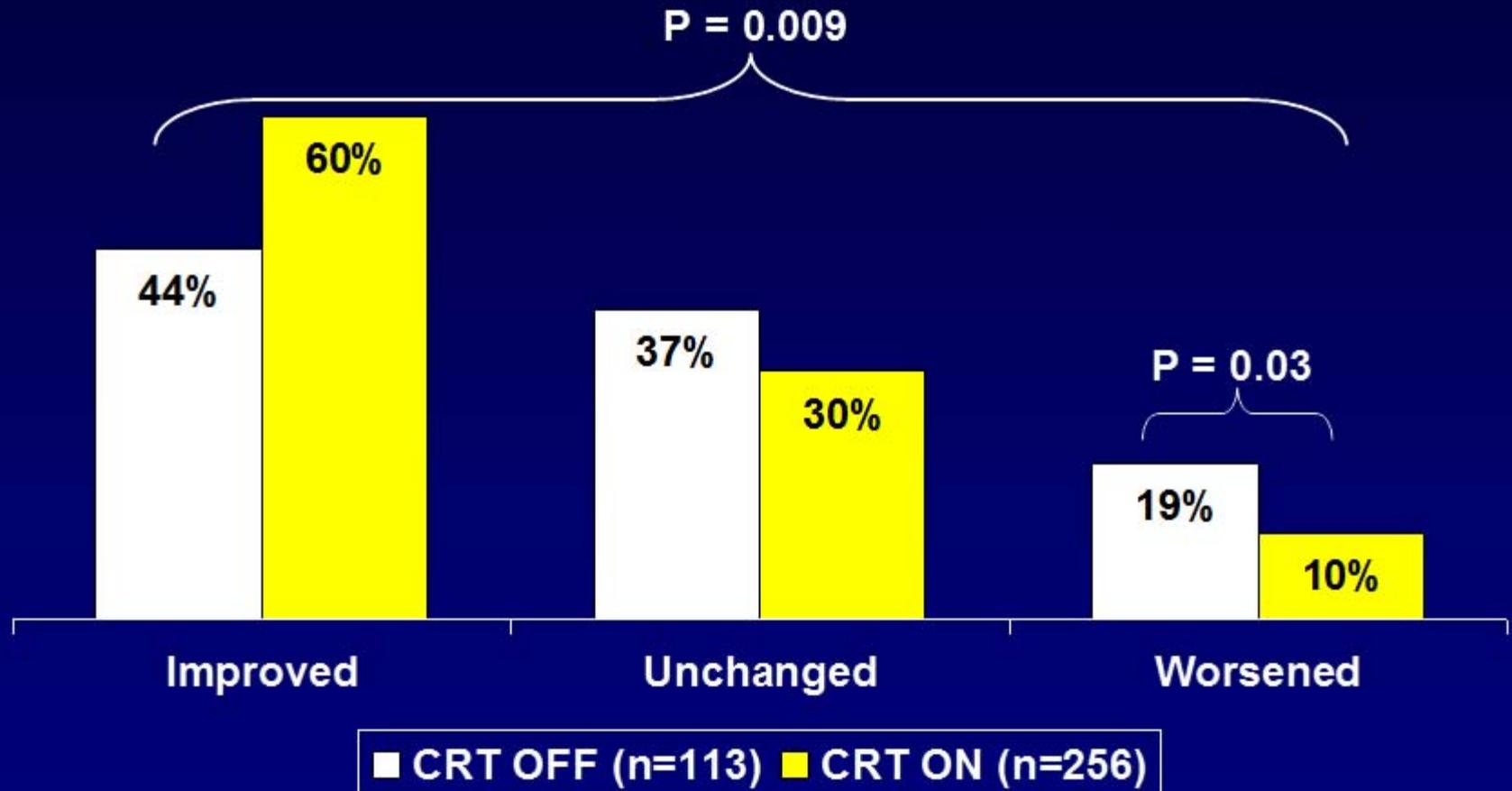
# RAFT NYHA Class II: FDA Exploratory Analysis of Primary endpoint – HF hospitalization or All-cause mortality

## FDA's 'less sick' population

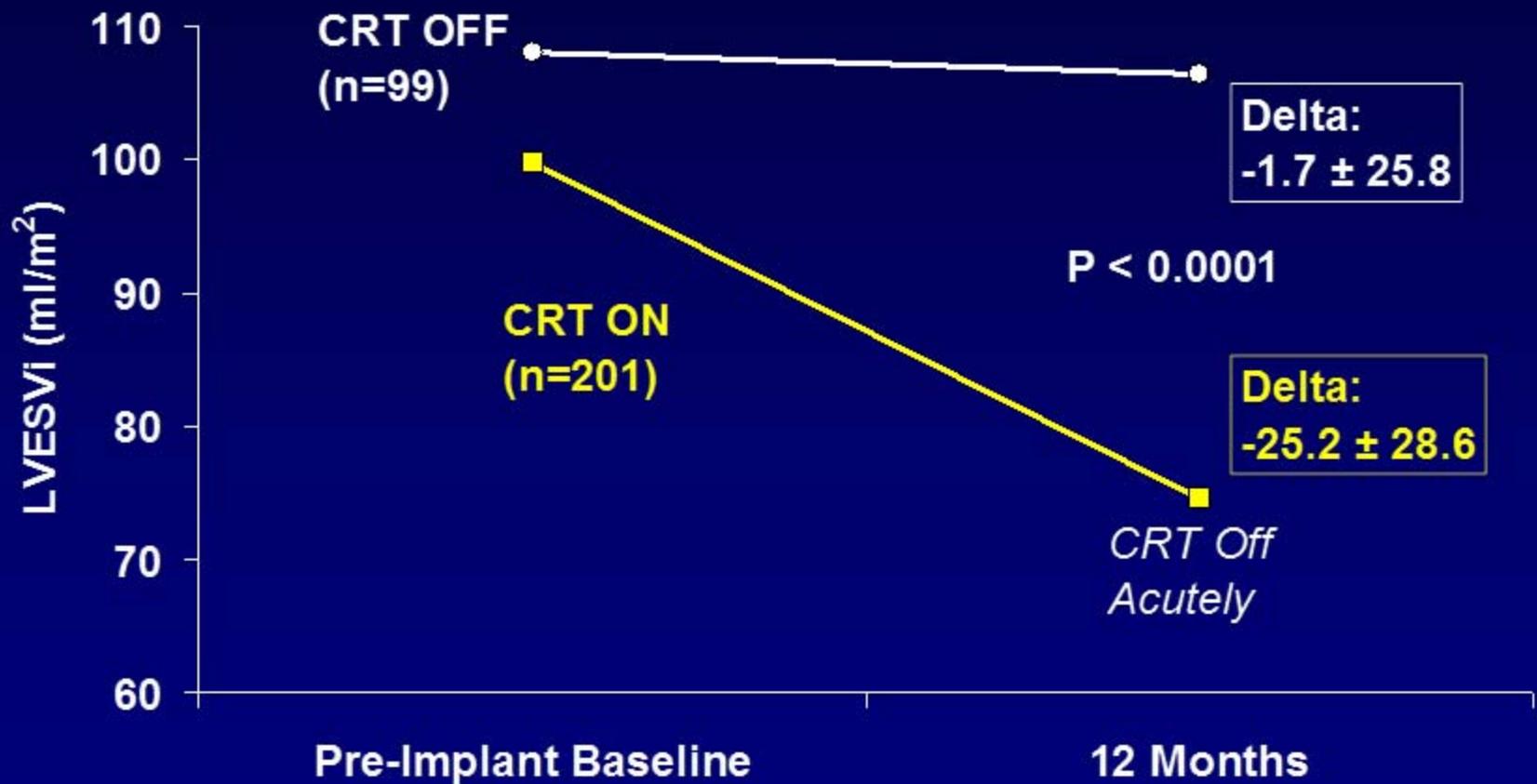
- No previous HF hospitalization
- 6 minute hall walk > 230
- Remove missing 6 minute hall walk

	n	HR (95% CI)	p-value
	862 (60% of NYHA II)	0.86 (0.66, 1.13)	0.275
Proposed patient population	561	0.70 (0.49, 0.999)	0.05

# REVERSE Clinical Composite at 12 Months – LBBB Subjects

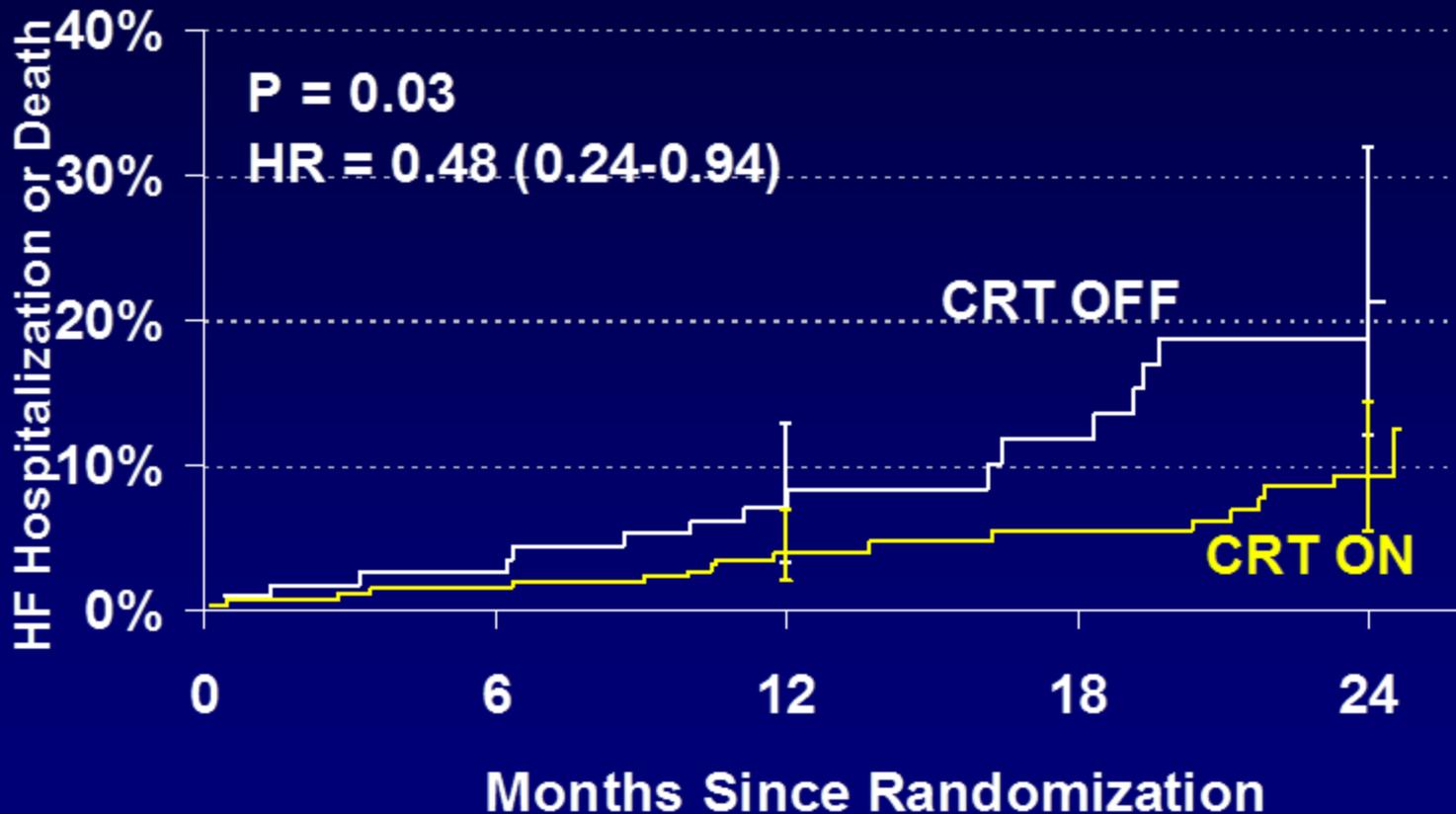


# REVERSE Reduction in Left Ventricular End Systolic Volume Index (LVESVi) LBBB Subjects



Analysis includes only paired data

# REVERSE: Significant Reduction in HF Hospitalization or All-cause Death - LBBB Subjects



Number 113  
remaining 256

110  
251

79  
187

51  
126

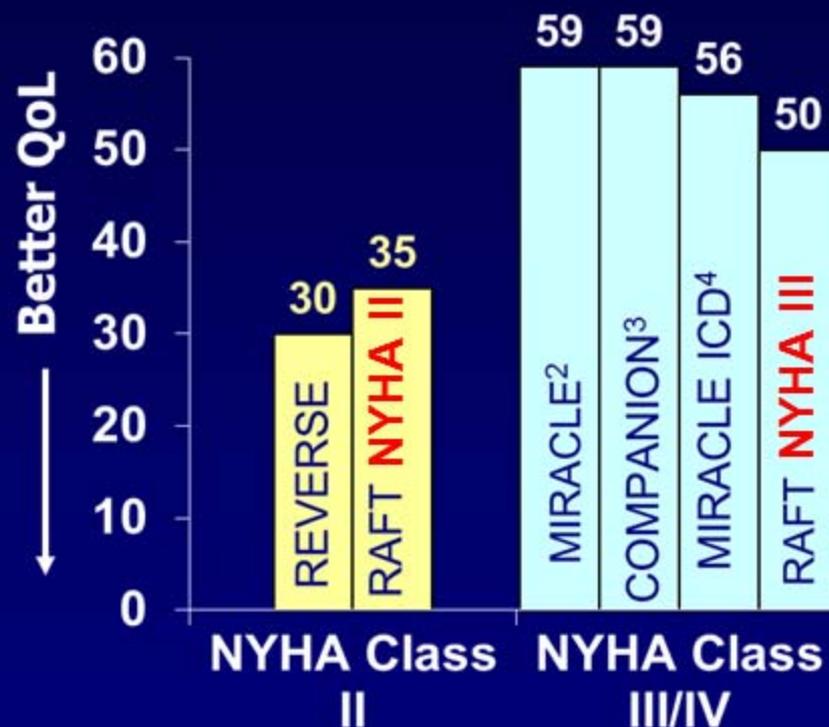
31  
55

# REVERSE and RAFT Exercise Capacity and Quality of Life Consistent with Milder Symptoms

Baseline Mean 6 Minute Walk Distance



Baseline Mean Minnesota Living with HF Score



\* 15% of MADIT CRT = NYHA Class I

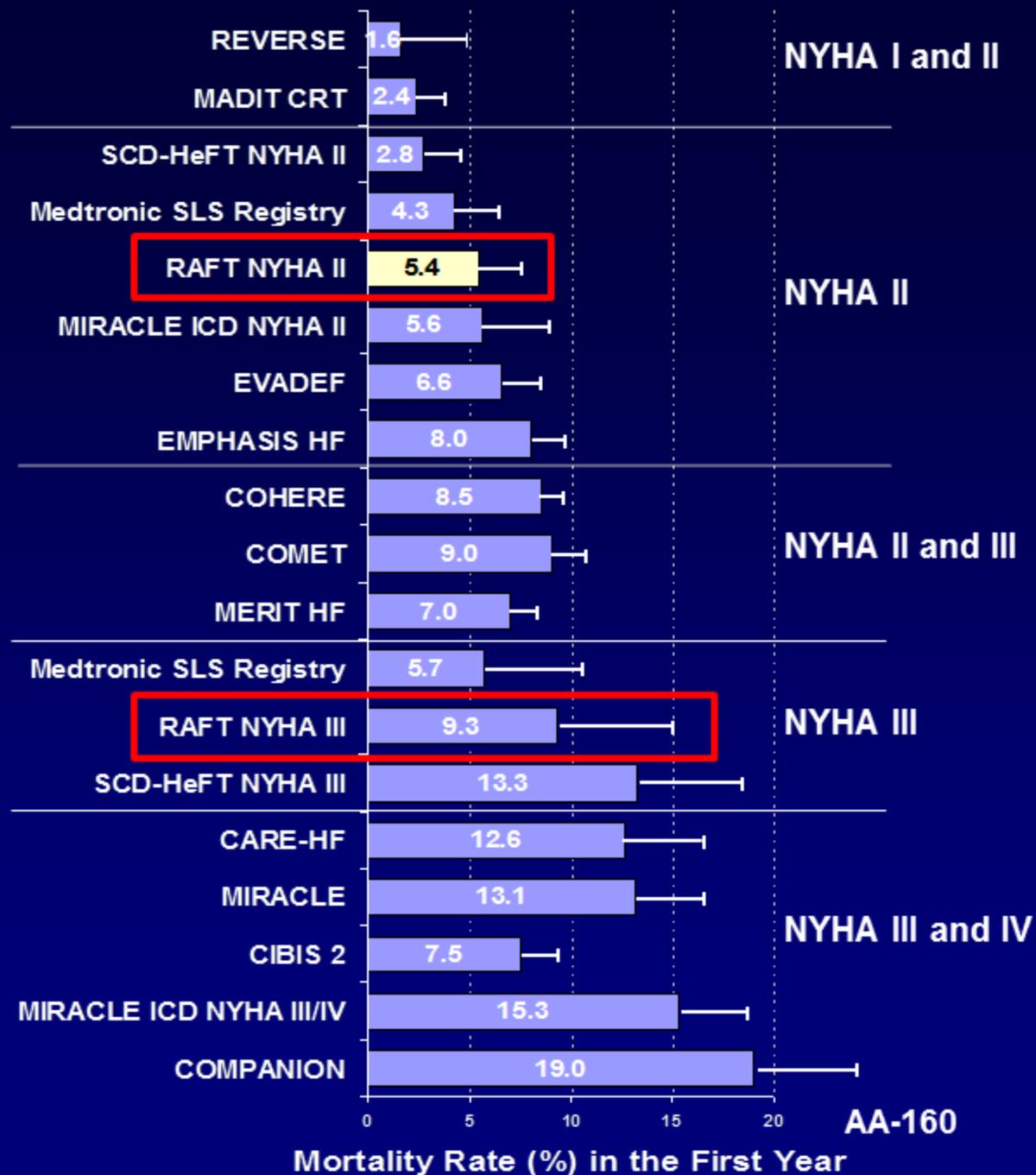
<sup>1</sup>Moss AJ, et al. N Engl J Med 2009;361:1329-38

<sup>2</sup>Medtronic (2002). InSync Cardiac Resynchronization System Final Report

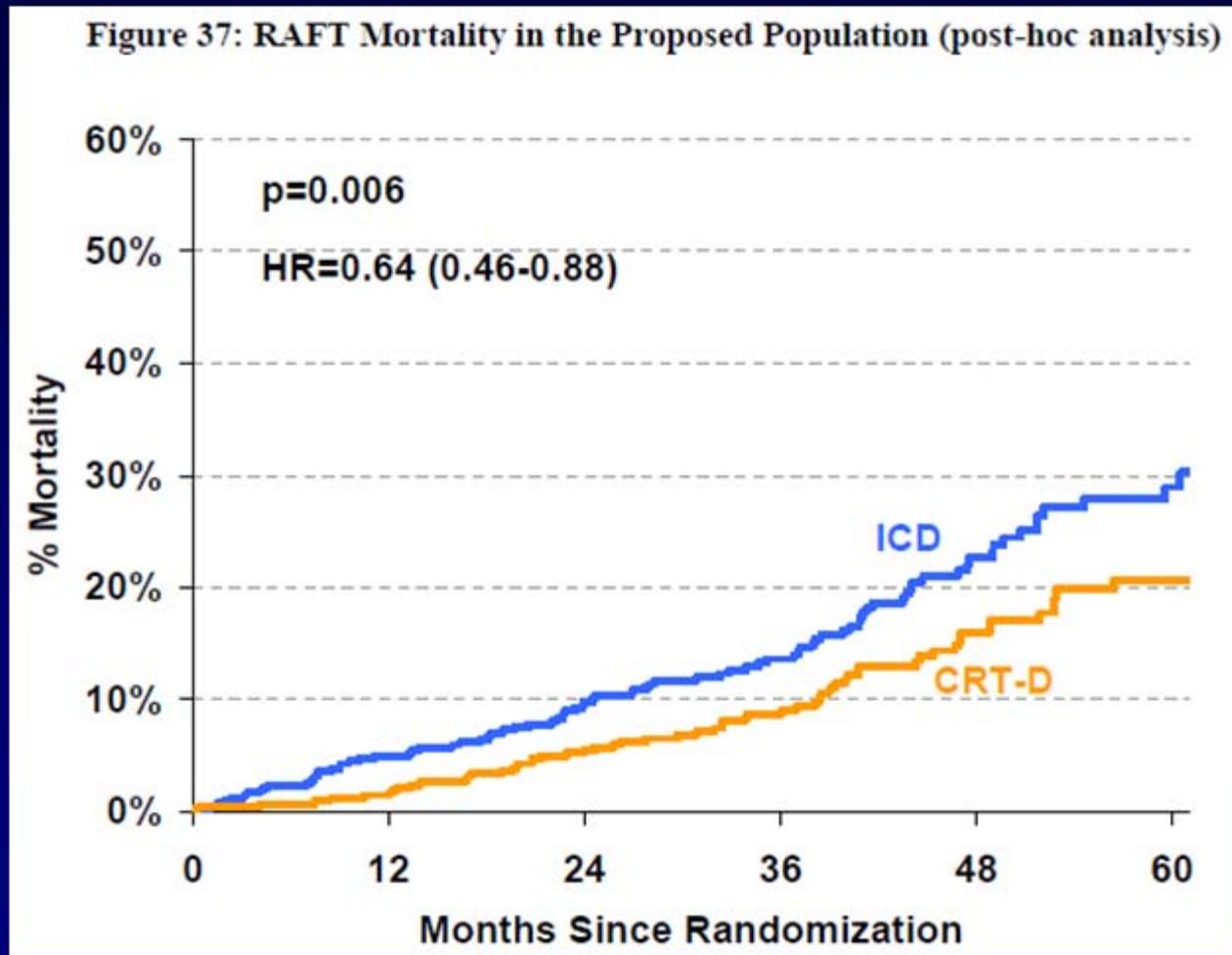
<sup>3</sup>Bristow BR, et al. N Engl J Med 2004; 350: 2140-2150

<sup>4</sup>Medtronic Model 7272 InSync ICD Cardiac Resynchronization System Final Clinical Report

# Comparison of Mortality Rates Over Time Between Trials

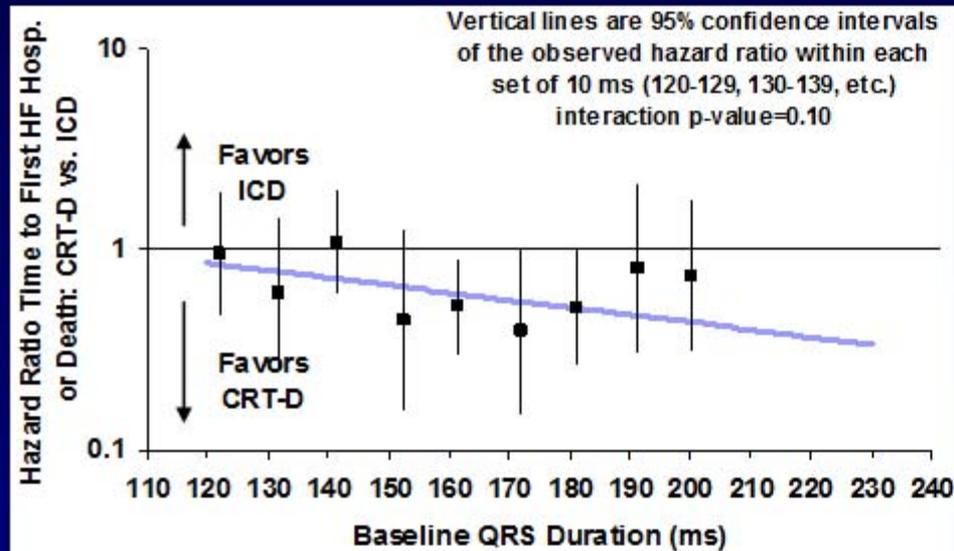


# Figure 37: RAFT Mortality in the Proposed Population (post-hoc analysis)

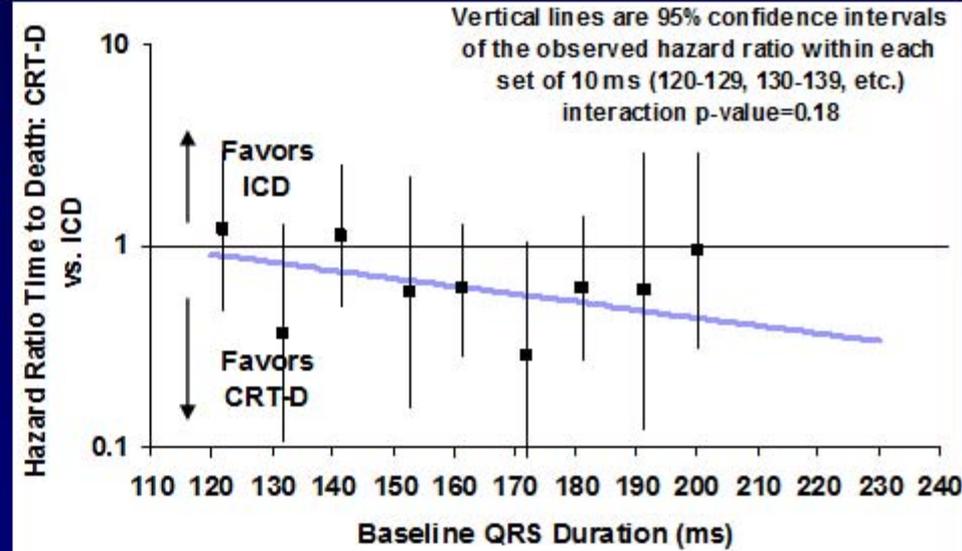


# QRS Analysis in RAFT Proposed Population

## HF Hospitalization or All-cause Death

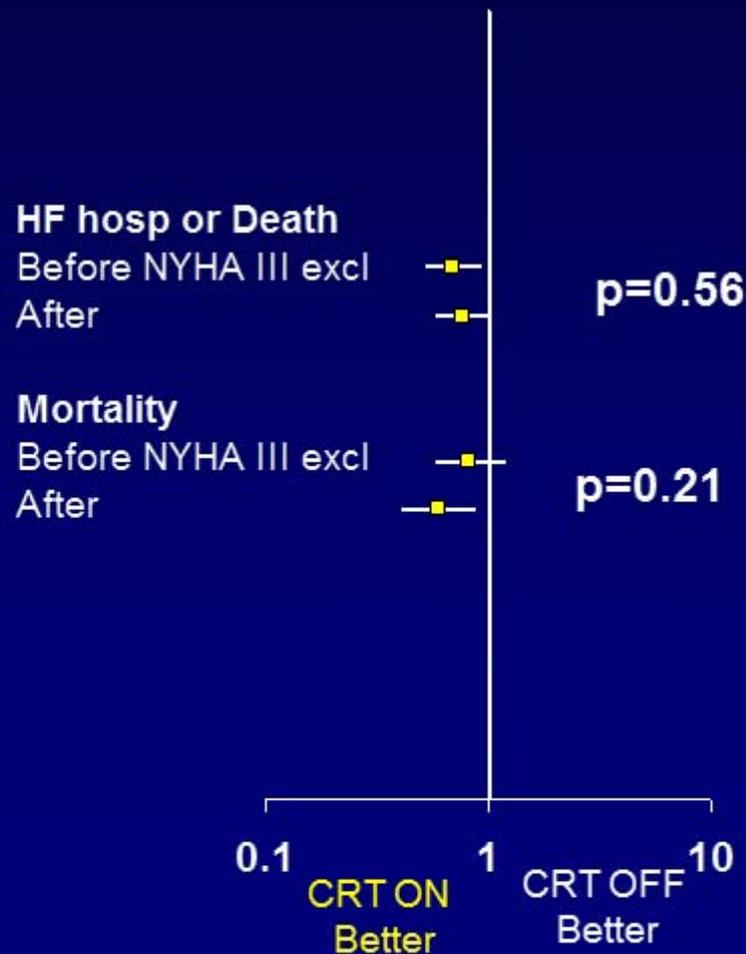


## All-cause Death



# RAFT NYHA II: Primary and Secondary Endpoint Before and After NYHA III Excluded

Hazard Ratio with 95% CI



# RAFT PPP: Balanced Distribution of Baseline Characteristics

Patient Characteristics	CRT-D (N=477)	ICD (N=470)	p-value
Age	65.0 ± 9.5	65.0 ± 9.1	0.9790
Male	79(17%)	95(20%)	0.1543
Ischemic	304(64%)	274(58%)	0.0957
LVEDF	22.4 ± 5.3	22.6 ± 5.1	0.5607
QRS	159.6 ± 24.6	162.3 ± 24.6	0.0948
ACE-I/ARBs	457(96%)	457(97%)	0.2881
Beta-blockers	440(92%)	421(90%)	0.1748
Myocardial infarction	267(56%)	233(50%)	0.0547
Hypertension	225(47%)	206(44%)	0.3277
Diabetic	147(31%)	154(33%)	0.5306
Creatinine (mg/dL)	1.2 ± 0.6	1.2 ± 0.7	0.9073
GFR	62.5 ± 19.4	64.3 ± 22.7	0.1859
Supine systolic blood pressure (mmHg)	118.6 ± 17.3	118.4 ± 17.0	0.8562
Supine diastolic blood pressure (mmHg)	68.5 ± 10.3	68.8 ± 10.0	0.6443

# REVERSE PPP: Balanced Distribution of Baseline Characteristics

Patient Characteristics	OFF (N=64)	ON (N=125)	p-value
Age at enrollment (years)	59.3 ± 12.6	63.2 ± 11.6	0.0371
Male	46(72%)	95(76%)	0.5973
Ischemic	22(34%)	56(45%)	0.2118
LVEF	22.9 ± 5.5	22.7 ± 5.2	0.8265
QRS	165.7 ± 21.0	162.8 ± 20.5	0.3626
ACE-I/ARBs	62(97%)	122(98%)	1.0000
Beta-blockers	59(92%)	121(97%)	0.1694
Myocardial infarction	19(30%)	46(37%)	0.4187
Hypertension	31(48%)	61(49%)	1.0000
Diabetes	19(30%)	22(18%)	0.0640
Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3	0.8212
GFR	76.9 ± 27.8	71.8 ± 23.1	0.1847
Supine systolic blood pressure (mmHg)	123.8 ± 18.4	125.0 ± 18.3	0.6682
Supine diastolic blood pressure (mmHg)	71.5 ± 12.9	71.9 ± 10.8	0.8548

## Table 29: Baseline Characteristics of Proposed Patient Population: REVERSE and RAFT

Table 29: Baseline Characteristics of Proposed Patient Population: REVERSE and RAFT

	REVERSE (n=189)	RAFT (n=947)
Age (yrs)	61.9 ± 12.0	65.0 ± 9.3
Male	75%	82%
Ischemic	41%	61%
LVEF (%)	22.8 ± 5.3	22.5 ± 5.2
Minnesota Living with HF Score	29.3 ± 20.0	34.6 ± 21.3
6-minute Hall Walk (m)	400 ± 117	373 ± 105
QRS Duration (ms)	164 ± 21	161 ± 25
On ACE-I/ARBs	97%	97%
On beta blocker	95%	91%
On diuretics	80%	81%
On lipid-lowering agent	58%	75%
On Digitalis/cardiac glycosides	31%	30%
Coronary artery disease	41%	51%
Myocardial infarction	34%	53%
Hypertension	49%	46%
Previous CABG	19%	30%
Diabetes	22%	32%
Serum Creatinine (mg/dL)	1.1 ± 0.3	1.2 ± 0.7
eGFR (mL/min/1.73m <sup>2</sup> )	73.6 ± 24.8	63.4 ± 21.1
Systolic Blood Pressure (mmHg)	124.6 ± 18.3	118.5 ± 17.1
Diastolic Blood Pressure (mmHg)	71.8 ± 11.5	68.7 ± 10.2

## **RAFT Mortality Before and After CIP V4 (1-27-06) change (All Subjects)**

	<b>Before</b>		<b>After</b>	
	<b>CRT-D</b>	<b>ICD</b>	<b>CRT-D</b>	<b>ICD</b>
<b>1 year</b>	<b>6.1</b>	<b>7.5</b>	<b>2.9</b>	<b>5.0</b>
<b>2 year</b>	<b>13.0</b>	<b>13.8</b>	<b>6.2</b>	<b>10.5</b>
<b>3 year</b>	<b>17.8</b>	<b>22.1</b>	<b>10.3</b>	<b>15.6</b>
<b>4 year</b>	<b>23.4</b>	<b>31.1</b>	<b>18.1</b>	<b>24.4</b>