



**Proposed Expansion of Indications  
for Medtronic's CRT-D Devices  
based on  
REVERSE and RAFT Studies**

**FDA Review of P010031 / S232**

**Ken Skodacek  
Division of Cardiovascular Devices  
Office of Device Evaluation  
Food and Drug Administration  
December 7, 2011**



# Members of FDA Team

## Office of Device Evaluation Staff

- Ken Skodacek
- Kimberly Selzman, MD, MPH
- Ileana Piña, MD, MPH
- Mitchell Shein, MS

## Office of Surveillance and Biometrics Staff

- Raj Nair, PhD
- Shaokui Wei, MD, MPH



# Commercially Available Devices

- Concerto CRT-D Model C154DWK (P010031/S031)
- Consulta CRT-D Model D224DRK (P010031/S084)
- Maximo II CRT-D Model D284TRK (P010031/S084)
- Concerto II CRT-D Model D274TRK (P010031/S125)
- Protecta XT CRT-D Model D314TRG (P010031/S171)
- Protecta CRT-D Model D334TRG (P010031/S171)



# Proposed Indications

The [name of device family] CRT-D system is indicated for heart failure patients who meet any of the following classifications:

- New York Heart Association (NYHA) Functional Class III or IV who remain symptomatic despite stable, optimal medical therapy, and who have a left ventricular ejection fraction  $\leq 35\%$  and a prolonged QRS duration.
- NYHA Functional Class II who remain symptomatic despite stable, optimal medical therapy, and who have left bundle branch block (LBBB) with a QRS duration  $\geq 120$  ms, and left ventricular ejection fraction  $\leq 30\%$ .

# Proposed Claims

- Medtronic CRT-D devices reduce all-cause mortality in NYHA Class II patients who remain symptomatic despite stable, optimal medical therapy and who have left bundle branch block, a QRS  $\geq 120$  ms, and a left ventricular ejection fraction  $\leq 30\%$
- Medtronic CRT-D devices reduce heart-failure hospitalizations in NYHA Class II patients who remain symptomatic despite stable, optimal medical therapy and who have left bundle branch block, a QRS  $\geq 120$  ms, and a left ventricular ejection fraction  $\leq 30\%$
- Medtronic CRT-D devices reduce heart-failure hospitalizations or all-cause mortality in NYHA Class II patients who remain symptomatic despite stable, optimal medical therapy and who have left bundle branch block, a QRS  $\geq 120$  ms, and a left ventricular ejection fraction  $\leq 30\%$

# Benefits & Risks

## Potential Benefits

- Improvement in Clinical Composite Response
- Reduction in heart failure hospitalizations
- Reduction in mortality

## Potential Risks

- Adverse events related to implant procedure for LV lead
- Adverse events related to chronic implantation of LV lead

**LV = Left Ventricular**

# REVERSE: Primary Discussion Points

## Pivotal Study Data

- Failed primary endpoint
- Differences between US and OUS patient characteristics and results
- Difficulty interpreting secondary analyses
- Limitations in the evaluation of the Clinical Composite Response endpoint

# RAFT: Primary Discussion Points

## Supporting Study Data

- Higher than expected mortality rate compared to similar CRT trials
- Multiple revisions to the inclusion criteria and statistical analysis plans
- Limitations of previous hospitalization data and baseline NYHA Class data at enrollment
- High rate of unblinding and crossovers
- Limited monitoring and collection of protocol deviations

# Overall: Primary Discussion Points

## Both Studies

- Post-hoc analyses of the proposed patient population
- Baseline doses and changes in doses of heart failure medications
- Totality of data from both studies does not support the proposed claims



# Primary Focus for Discussions

- Do the data and analyses support the proposed indication for use?
  
- Do the data and analyses support the proposed claims?

# Patient Groups

- REVERSE

- REVERSE Full Cohort n=610
- REVERSE NYHA II n=503 (82%)
- REVERSE-PPP n=189 (31%)

- RAFT

- RAFT Full Cohort n=1798
- RAFT NYHA II (prespecified) n=1438 (80%)
- RAFT-PPP n=947 (53%)

PPP = Proposed Patient Population



# FDA Presentations

- Kimberly Selzman – Clinical
- Raj Nair – Statistical
- Shaokui Wei – Epidemiology
- Ken Skodacek – Conclusions



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# REVERSE: Discussion Points

1. Baseline demographics and US / OUS poolability
2. HF medication dosing at baseline and during trial
3. Primary endpoint failed
4. Post-hoc analysis of HF hospitalization and mortality is difficult to interpret

# REVERSE: Study Overview

Study Design	Randomized, controlled, double blind
Enrollment Criteria	NYHA <b>Class I</b> , Class II, stage C QRS $\geq$ 120 ms and <b>LVEF <math>\leq</math> 40%</b> BB, ACE-I/ARB drug therapy stable for 30 days
Enrolling Sites	37 US sites (n=343) 36 outside the US sites (n=267)
Randomization Enrollment	2:1; 610 subjects randomized; 419 CRT ON 191 CRT OFF
Primary Objective	Clinical Composite Response (CCR); Proportion of subjects “worsened” in each arm at 12 months

# REVERSE Baseline Demographics

## OUS and US Differences

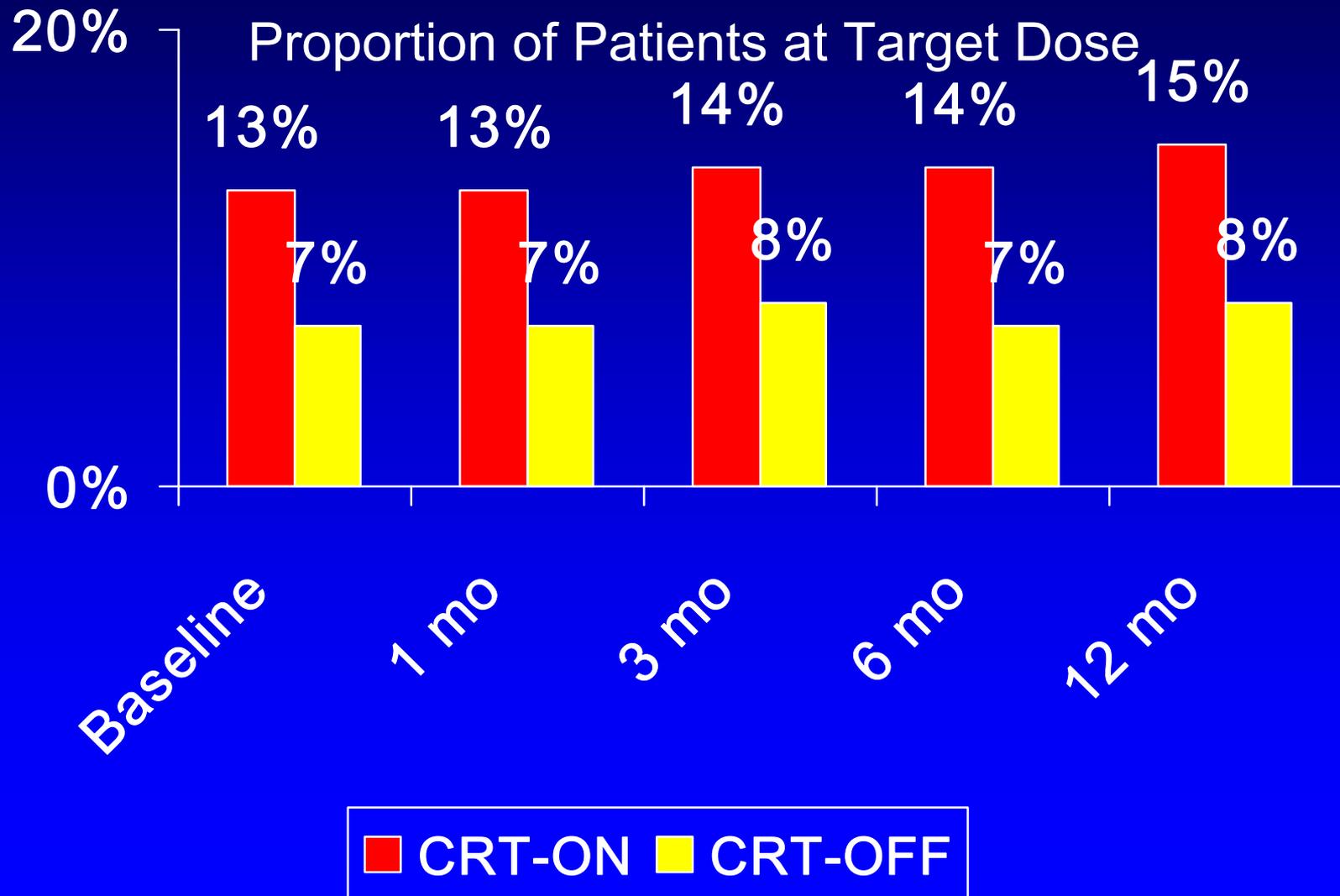


	<b>OUS</b> n=267 (24 mo)	<b>US</b> n=343 (12 mo)
LVEF (%)	27.1	26.3
NYHA Class II	82%	83%
QRS duration (ms)	156	151
History of hypertension	34%	66%
Ischemic	44%	63%
Previous myocardial infarction	34%	55%
QRS morphology		
Left Bundle Branch Block	72%	52%
Right Bundle Branch Block	5%	13%
IVCD	22%	36%

# REVERSE Baseline HF Medications

Target Dose	$\geq 100\%$ target	$\geq 50\%$ target	$< 25\%$ target
<b>Beta Blocker</b> Carvedilol 50 mg/day or equivalent	23%	54%	<b>23%</b>
<b>ACE-I / ARB</b> Lisinopril 40 mg/day Losartan 100 mg/day or equivalent	11%	48%	<b>20%</b>

# REVERSE ACE-I/ARB Doses Higher in the CRT-ON Arm



# REVERSE Baseline HF Medications

## OUS and US Differences

	<b>OUS</b> n=267	<b>US</b> n=343
<b>ACE-I/ARB</b>		
% using	97%	88%
% at or above target dose	6%	15%
Mean daily dose (mg)	16.3 ± 9.0	15.9 ± 14.5



# REVERSE

## Overall Concerns about Medication Use

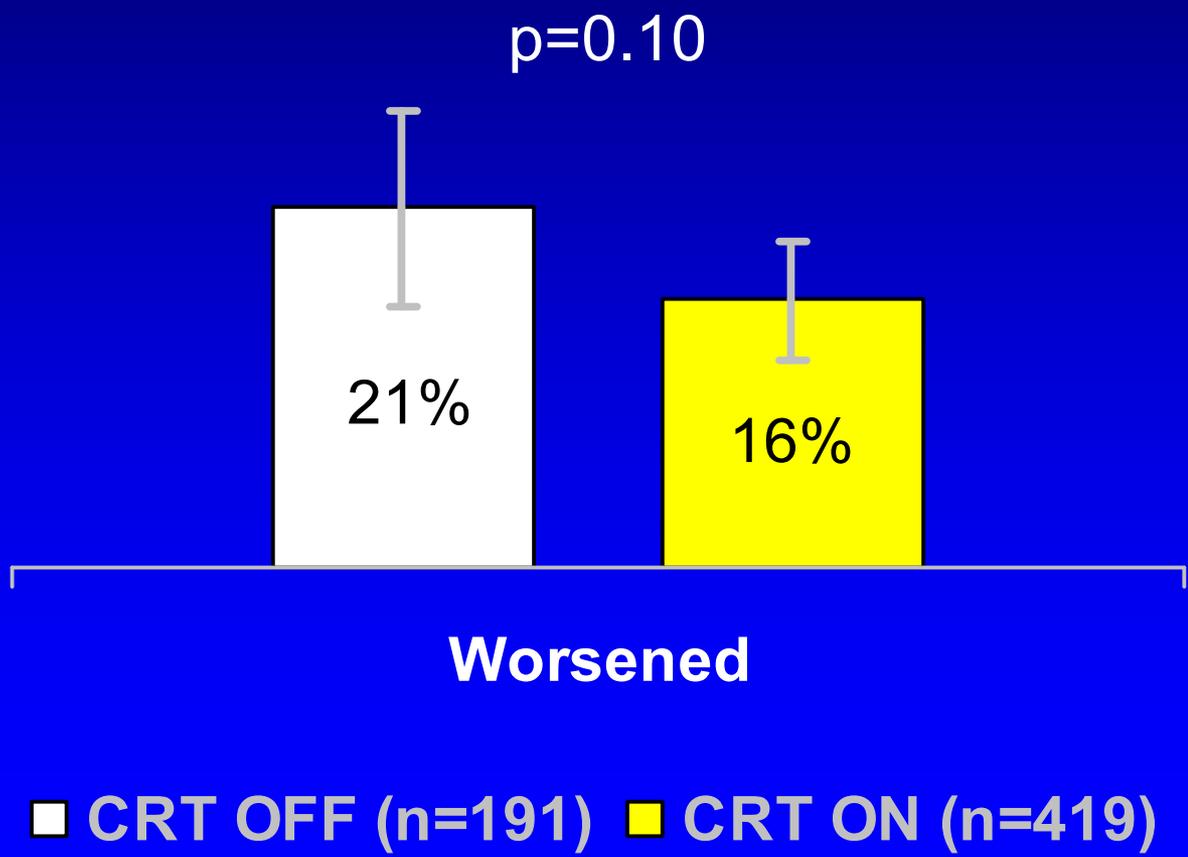
- Low doses of HF medications
- Lower doses of ACE/ARB in CRT-OFF group
- Lower ACE/ARB use in OUS patients



# REVERSE Primary Effectiveness Endpoint

## Clinical Composite Response

### (Proportion Worsened)



# REVERSE: Primary Endpoint Clinical Composite Response (CCR) Key Components

Subjects categorized Improved, Unchanged, or Worsened

WORSENERD if

- Death or Overnight HFH
- Stops double blind treatment due to worsening HF
- Worsened NYHA class
- *Moderately or Markedly Worse* on **Patient Global Assessment**
  - Markedly improved
  - Moderately improved
  - Slightly improved
  - The same
  - Slightly worse
  - Moderately worse
  - Markedly worse

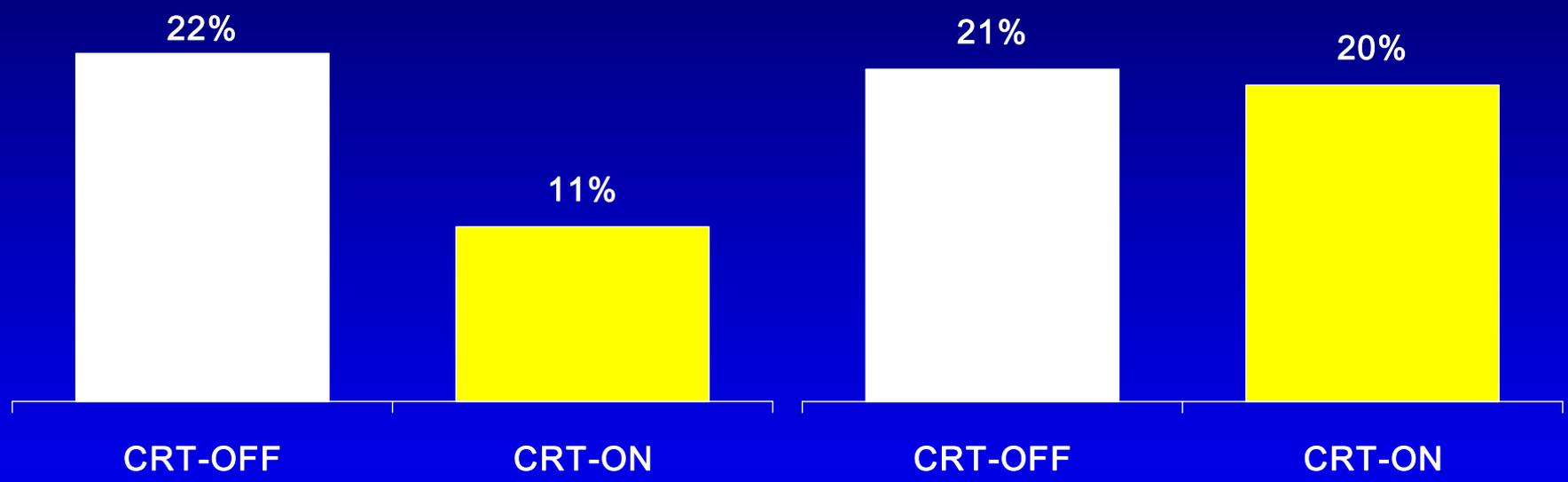


# REVERSE Full Cohort (n=610)

## Primary Endpoint: CCR Worsened at 1 year

### OUS CCR Worsened

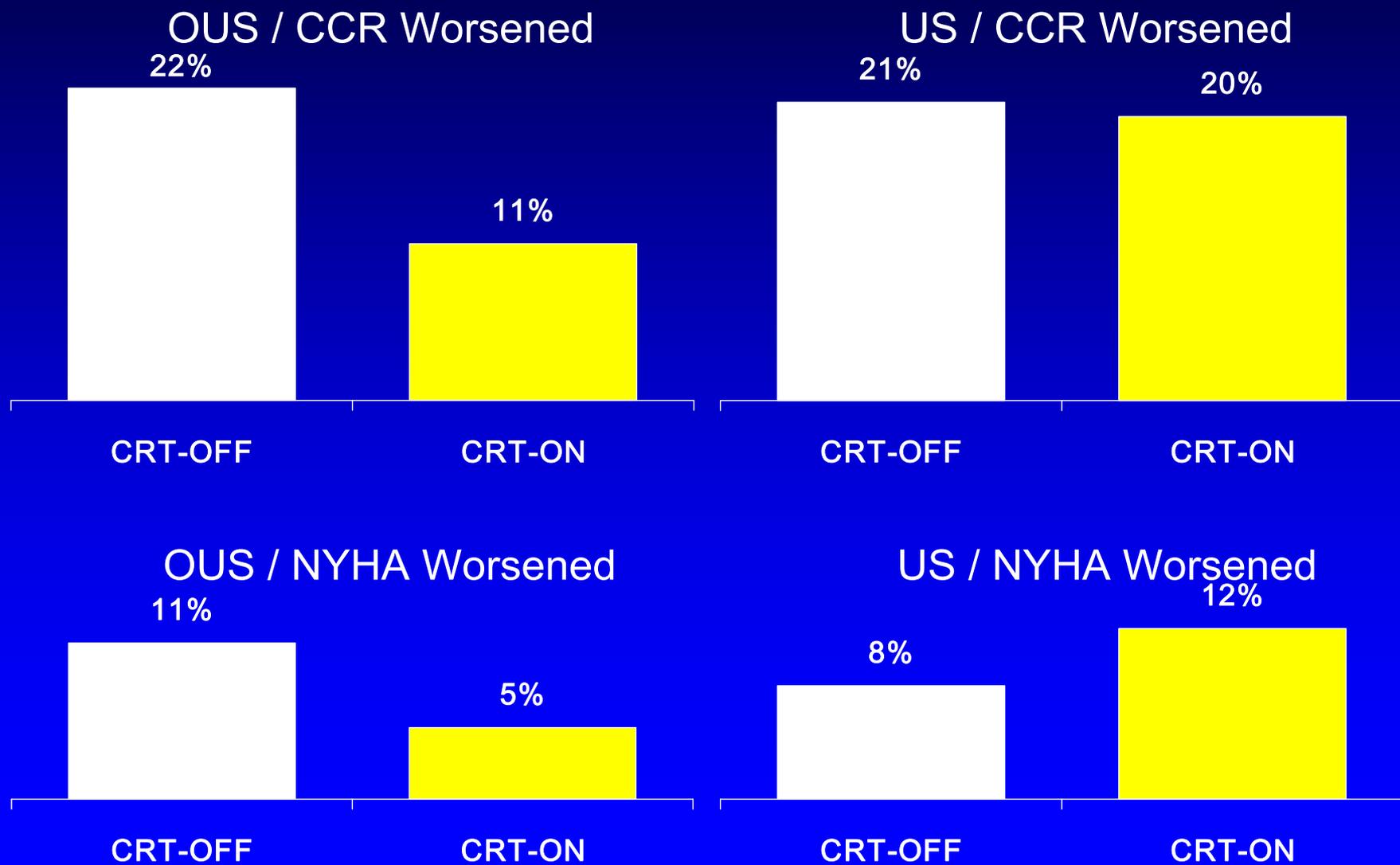
### US CCR Worsened



Note small number of patients

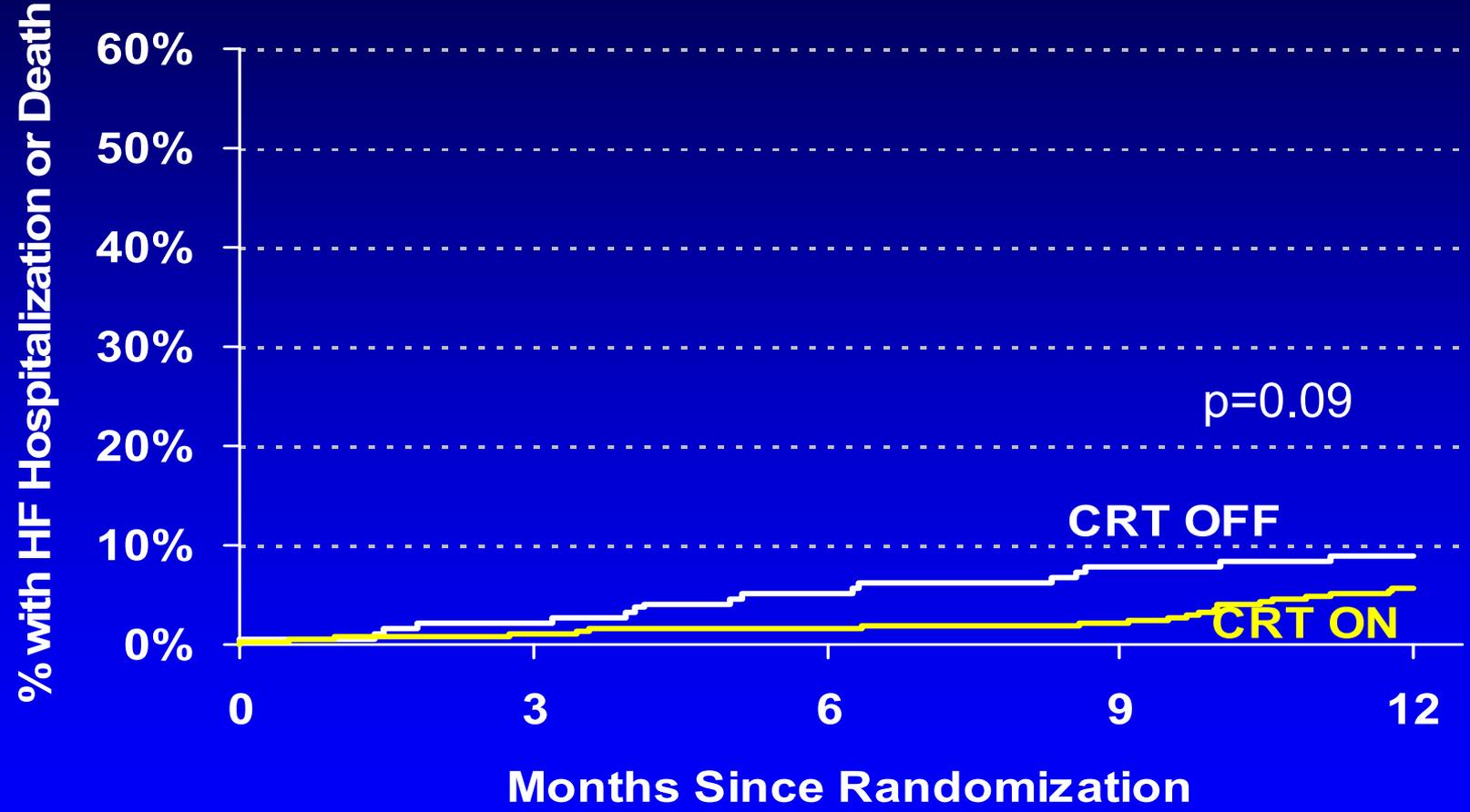
# REVERSE Full Cohort (n=610)

## Primary Endpoint CCR and NYHA Class





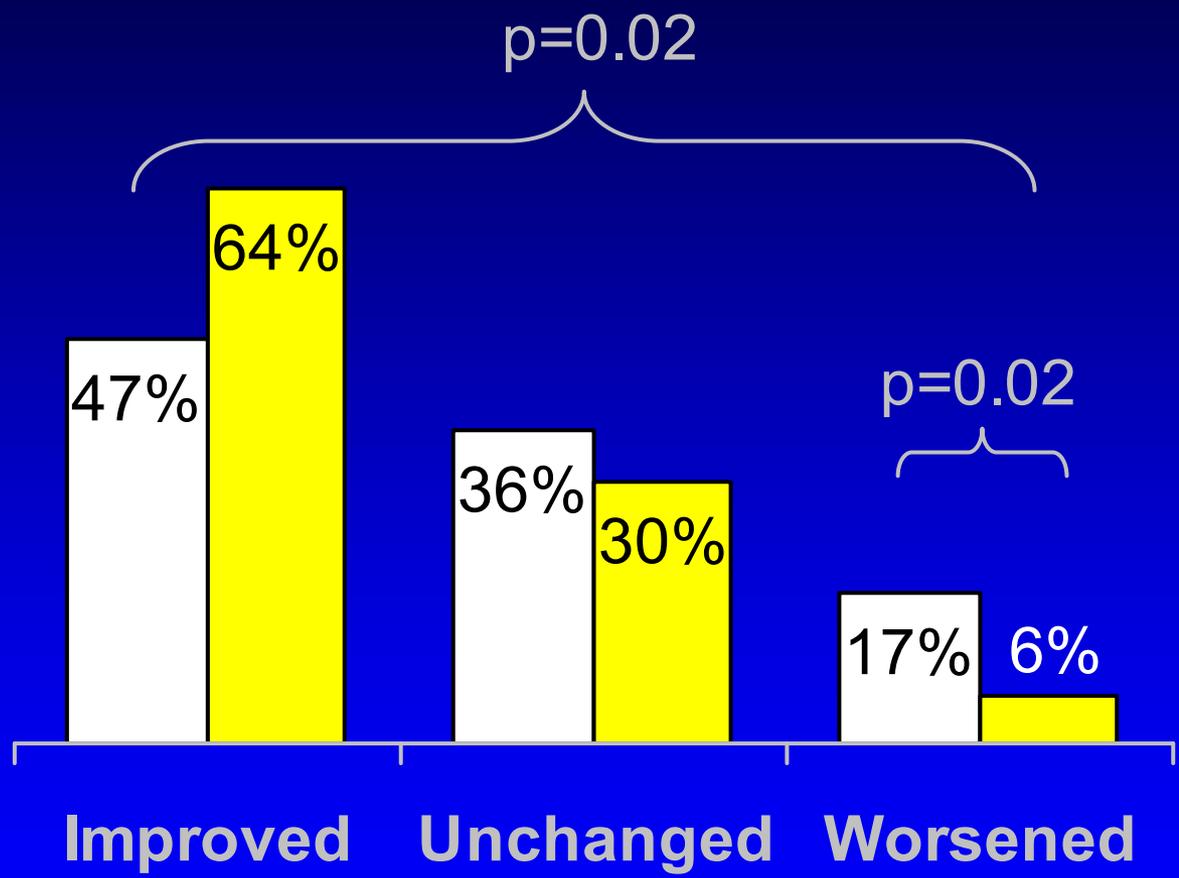
# REVERSE Full Cohort (n=610) Post-Hoc Time to First HFH or All-Cause Mortality at 12 Months



Number	191	181	126
remaining	419	412	282



# REVERSE-PPP (n=189) CCR at 12-Months (Post-Hoc)

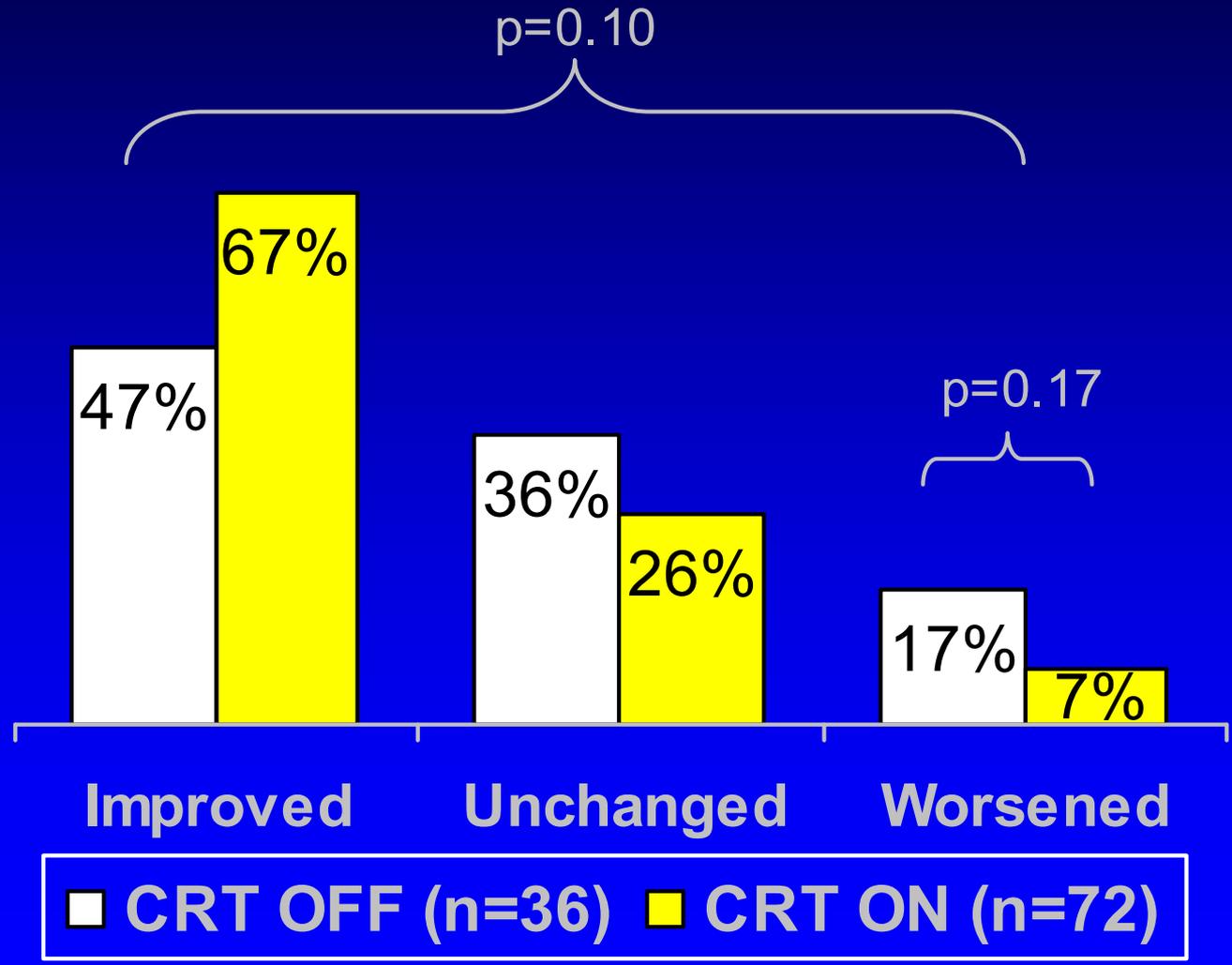


4 Deaths  
7 HF Hosp

■ CRT OFF (n=64) ■ CRT ON (n=125)



# REVERSE-PPP US Only (n=108) CCR at 12-Months (Post-Hoc)





## LVESVi as a Clinical Surrogate

LVESVi showed a difference between CRT ON and CRT OFF groups, however

- CRT-ON group did not have a significantly lower proportion of subjects Worsened at 12 months
- CRT-ON group did not have a reduction in all cause mortality

FDA Letter dated May 28, 2004

"However, FDA believes that determining whether changes in LVESVi correlate with changes in patient clinical status will be more relevant to assessing the value of LVESVi as a useful surrogate in future CRT trials. FDA anticipates that all relevant clinical data, in addition to the criterion specified in the protocol, will be necessary to make this assessment."

# REVERSE Full Cohort (n=610)

## Safety Analysis

- No prespecified primary safety endpoint
- Adverse events (AE) and deaths were collected
- LV lead-related AE rate: 21% at 48 months
  - Inappropriate device stimulation 11.1%
  - LV lead dislodgement 7.1%
  - Coronary sinus dissection 0.5%
- LV complication rate: 9.1% at 12 months

# RAFT: Discussion Points

1. Baseline demographics and comorbidities
2. HF medications dosing at baseline and during trial
3. All cause mortality rate was higher than similar trials and; 30% were non-cardiac deaths
4. Cardiovascular mortality demonstrated less of a treatment effect than all-cause mortality

# RAFT: Study Overview

Study Design	Randomized, controlled, double blind
Enrollment Criteria	NYHA Class II or III (later changed to II only) QRS $\geq$ 120 ms or paced $\geq$ 200 ms, LVEF $\leq$ 30% BB, ACE-I/ARB drug therapy stable for 6 weeks
Enrolling Sites	24 Canadian sites (n=1617) 7 European (n=135) 2 Australian sites (n=44) 1 Turkish site (n=2)
Randomization Enrollment	1:1; 1798 subjects (1438 NYHA Class II) 894 CRT 904 ICD (708 CRT and 730 ICD)
Primary Objective	Time to first heart failure hospitalization or all cause death

# RAFT NYHA II (n=1438)

## High Prevalence of Chronic Diseases

	RAFT NYHA II (n=1438)
Diabetes Mellitus	33%
% with GFR<60	47%
Permanent Atrial fib/flutter	11.5%
Prior HF Hospitalization	24%

	REVERSE NYHA II (n=503)
	24%
	32%
	0%
	0%



# RAFT - Minimal Data on Prior Heart Failure Hospitalization Collected

Hospitalization dates	Name of Hospital	Principle Discharge Diagnosis
<p>#1</p> <p>FROM: <input type="text"/> <input type="text"/></p> <p style="text-align: center;">Day                  Month                  Year</p> <p>TO: <input type="text"/> <input type="text"/></p> <p style="text-align: center;">Day                  Month                  Year</p> <p>Still hospitalized <input type="checkbox"/></p> <p><i>Please mark one:</i></p> <p><input type="radio"/> UNDER 24 HRS HOSPITALIZATION</p> <p><input type="radio"/> OVER 24 HRS HOSPITALIZATION</p>	<p>_____</p> <p>_____</p> <p>Name of Hospital if transferred:</p> <p>_____</p> <p>_____</p>	<p>ICD9 Diagnosis Code</p> <p><input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/></p> <p>If above not available, please insert Diagnosis Text:</p> <p>_____</p>

Very limited data was collected regarding prior heart failure hospitalizations

# RAFT NYHA II (n=1438)

## Evaluation of Prior HF Hospitalizations

Time to first HF hospitalization or all-cause death

		Hazard Ratio	95% confidence interval
Hosp for HF in previous 12 mo	ICD (n=168)	0.53	0.38 - 0.74
	CRT-D (n=177)		
<u>Not</u> Hosp for HF in previous 12 mo	ICD (n=562)	0.83	0.66 - 1.04
	CRT-D (n=531)		

# RAFT NYHA II (n=1438)

## Baseline Heart Failure Medications

Target Dose	$\geq 100\%$ target	$\geq 50\%$ target	$< 25\%$ target
<b>Beta Blocker</b> Carvedilol 50 mg/day or equivalent	16%	49%	<b>26%</b>
<b>ACE-I / ARB</b> Lisinopril 40 mg/day Losartan 100 mg/day or equivalent	10%	55%	<b>17%</b>

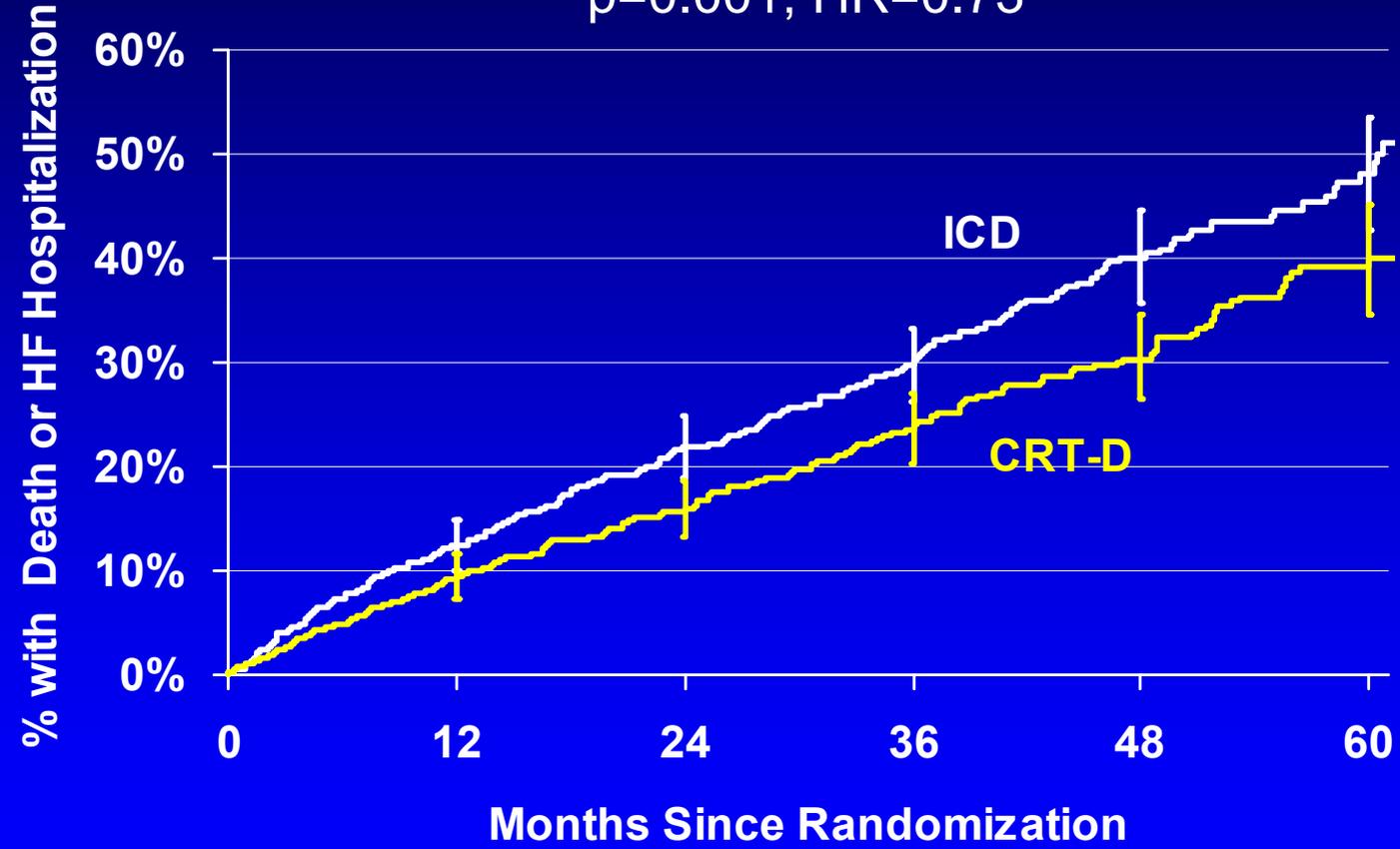


# RAFT NYHA II (n=1438)

## Primary Endpoint

### Time to first HF Hospitalization or All-Cause Mortality

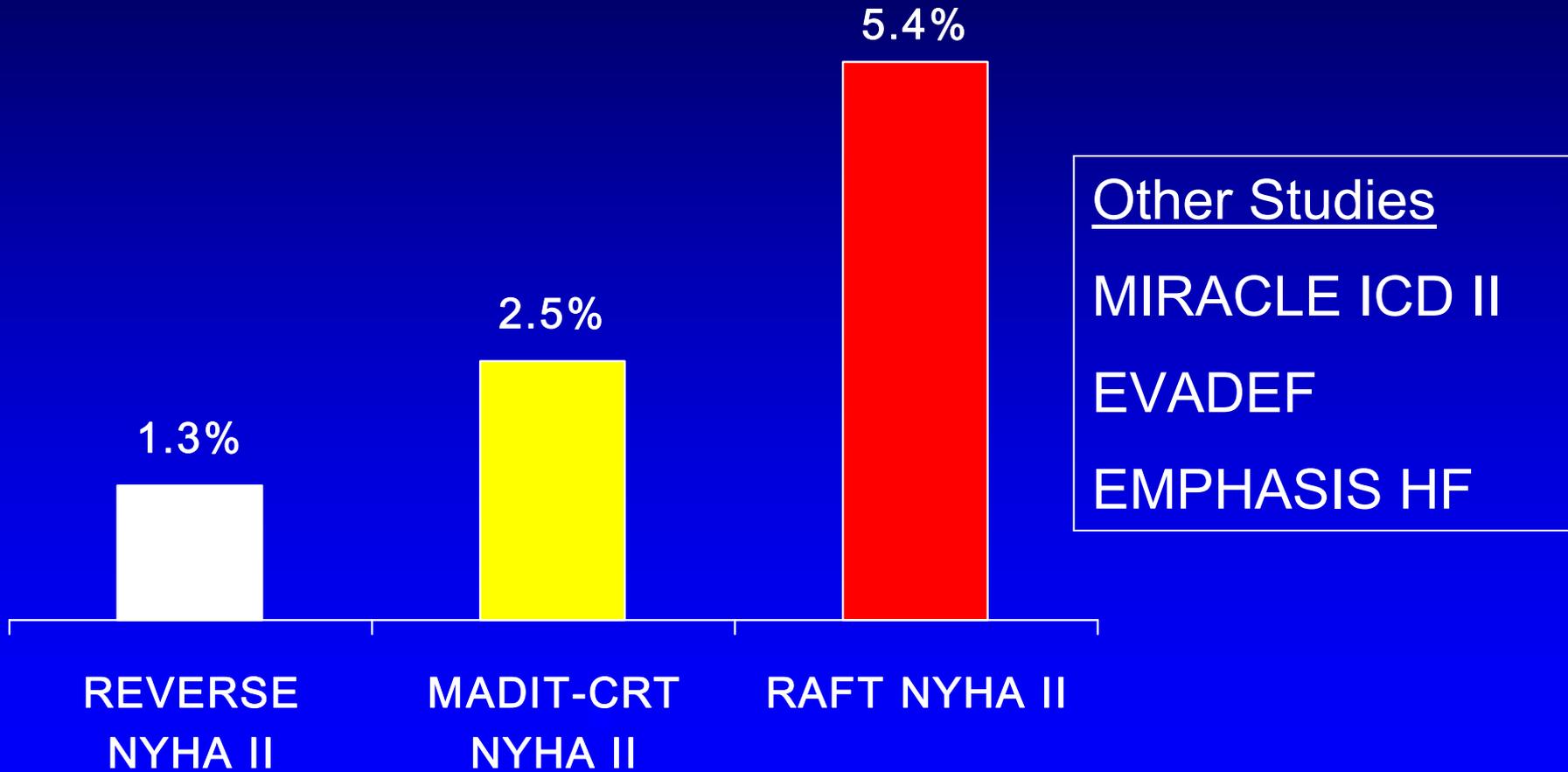
p=0.001, HR=0.73



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



# RAFT NYHA II (n=1438) Higher 12-Month Mortality Compared to Other CRT Trials



# RAFT NYHA II (n=1438)

## Total Mortality

	<b>ICD (n=730)</b>	<b>CRT-D (n=708)</b>
Total Deaths	154	110
Non-CV Deaths	49 (32% of total)	34 (31% of total)

# RAFT NYHA II (n=1438)

## Cardiovascular Mortality

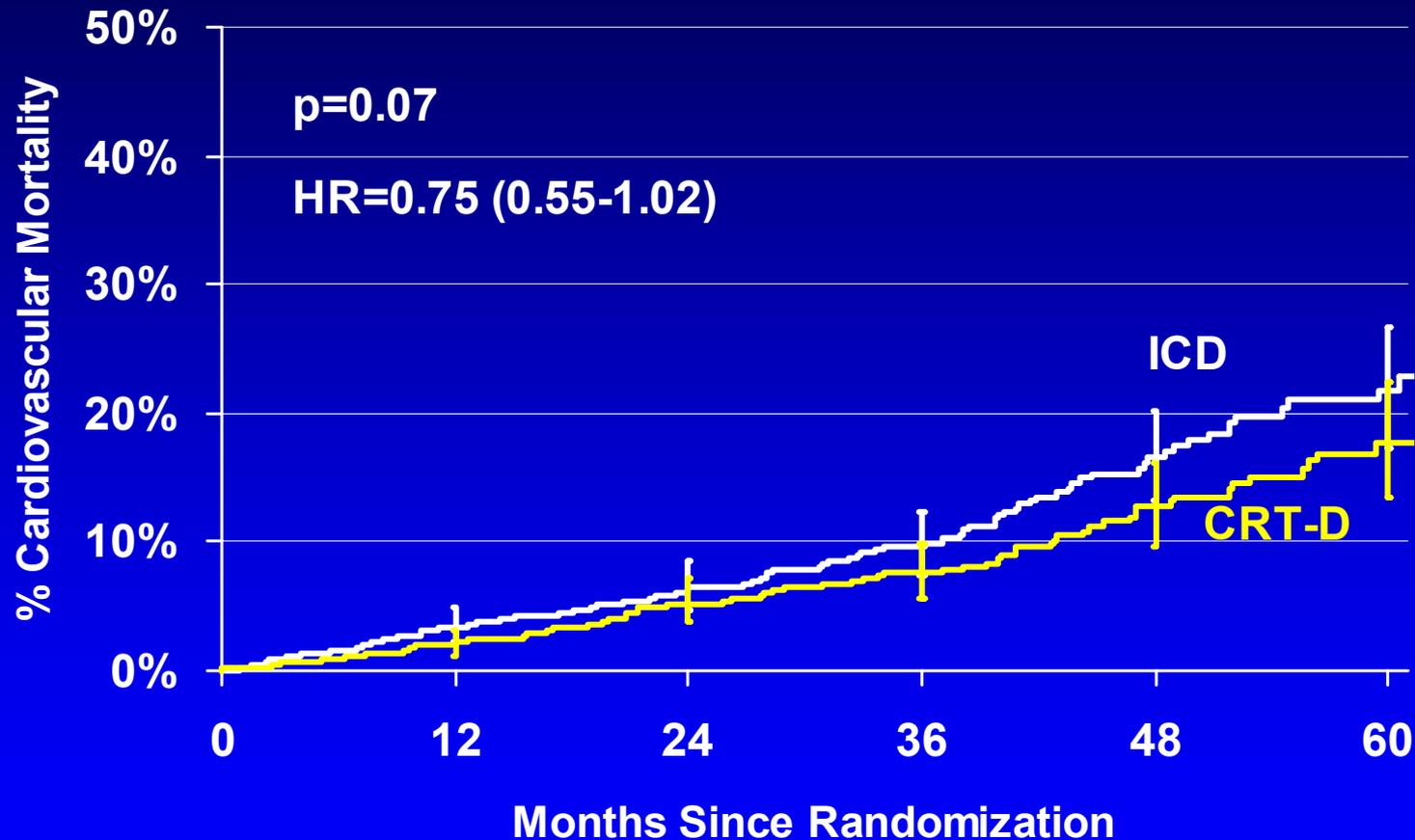
- Cardiovascular Mortality Definition (Key Components)
  - Unexpected death presumed to be CV disease
  - MI
  - CHF
  - Post CV intervention
  - Documented arrhythmia
  - Death due to other vascular diseases (aortic aneurysm)
  - Stroke

	ICD	CRT-D
Fatal Stroke	6 (10%)	4 (4%)



# RAFT NYHA II (n=1438)

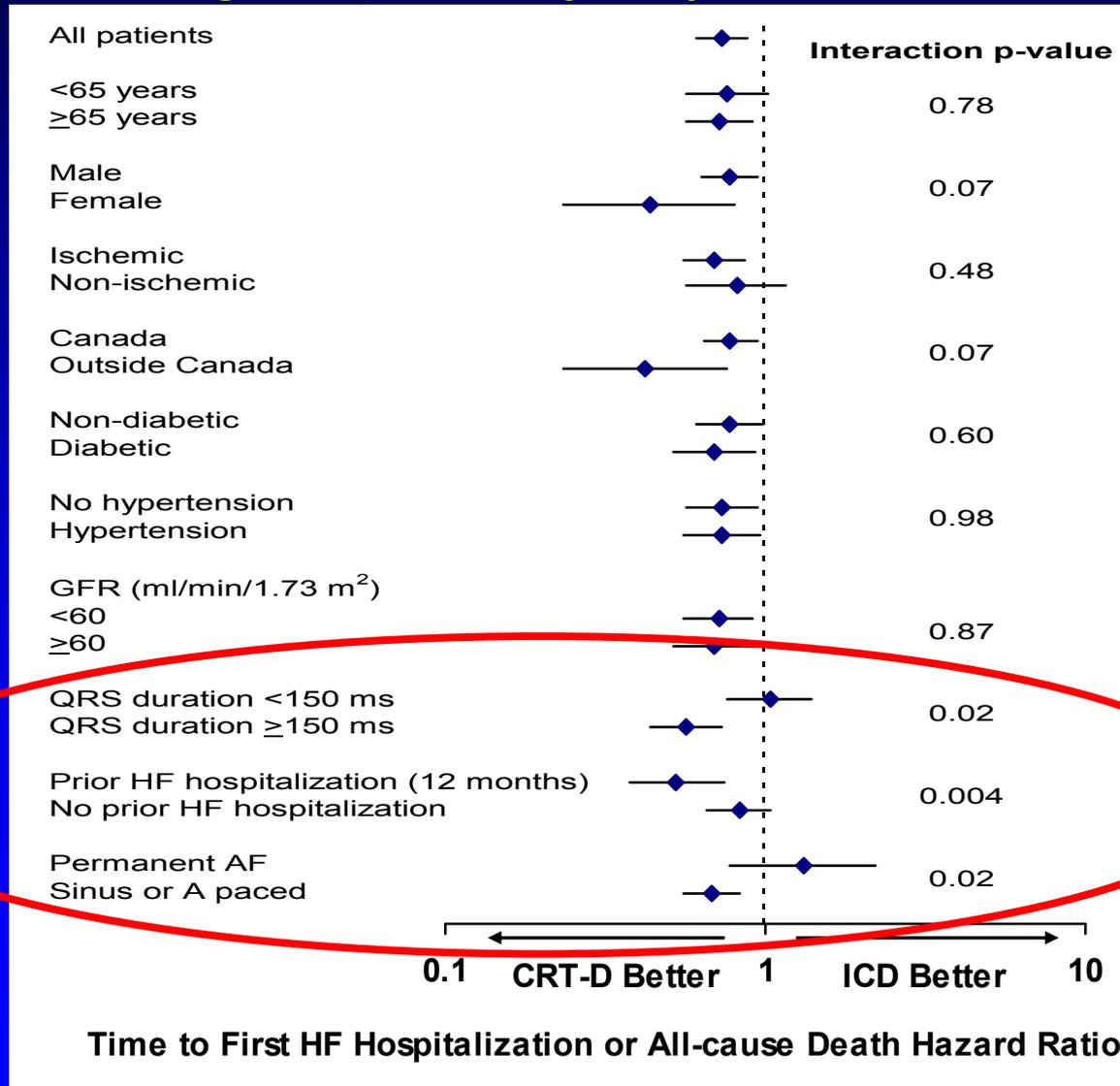
## CV Mortality Strokes Removed (Post-Hoc)



Number remaining	730	687	533	366	190	83
	708	679	530	361	207	89



# RAFT NYHA II (n=1438) Time to 1<sup>st</sup> HFH or Mortality (Post-Hoc Subgroup Analysis)





# RAFT Full Cohort Safety Analysis

(n=1787 attempted implants, 888 CRT-Ds)

- No prespecified primary safety endpoint
- Only Implant and System Related Complications (SRC) were collected
- 106 LV lead related Adverse Events in 10% (n=90) of subjects

LV lead dislodgements      8.1%

Pacing/sensing issues      1.6%



# REVERSE Study and Results

## Clinical Summary and Concerns

- Failed to meet its primary endpoint
- US and OUS subjects not poolable
- Post-hoc analyses looking at composite CCR distribution were not positive at 12 months for US
- The proposed patient population requires post-hoc analyses on a small subgroup of the entire cohort



# RAFT Study and Results

## Clinical Summary and Concerns

- Mortality is higher than other contemporary CRT trials
- Higher prevalence of comorbidities
- 25% with a recent HF hospitalization may select sicker, more symptomatic patients
- CV mortality not significantly different between treatment arms in Class II subgroup (excluding stroke)
- Proposed patient population requires post hoc analyses on a small subgroup of the entire cohort



# Proposed Claims Are Not Based on REVERSE and RAFT

*Medtronic CRT-D devices reduce heart-failure hospitalizations, reduce all cause mortality, and reduce heart-failure hospitalizations or all-cause mortality in NYHA Class II patients who remain symptomatic despite stable, optimal medical therapy and who have a [LBBB] a QRS  $\geq 120$  ms, and a [LVEF]  $\leq 30\%$*

- Majority of RAFT and REVERSE subjects were well below target dose and therefore not on OMT
- REVERSE did not show a mortality benefit
- The proposed population was not prespecified and is not readily identifiable from either trial



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Office of Surveillance and Biometrics  
Food and Drug Administration  
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# Discussion Items

1. REVERSE – Statistical design and major conclusions
2. RAFT – Issues with design / conduct and implications
3. Validity of post-hoc analyses upon which proposed indication is based

# Primary Endpoint (REVERSE)

## Composite Primary Endpoint

- Proportion of subjects with 'worsened' clinical composite response (CCR) at 12 months

## Objective

- Proportion 'worsened' in treatment (CRT ON) group is less than in control (CRT OFF) group

## Hypothesis (Superiority)

$$H_0: p_t = p_c$$

$$H_a: p_t \neq p_c$$

- Two-sided type I error rate of 0.05

# Primary Endpoint Evaluation (REVERSE)

- Primary analysis population
  - Intent-to-Treat (ITT): All randomized subjects
- Primary missing data imputation method:
  - Last observation carried forward (LOCF)

# Primary Endpoint Results (REVERSE)

- Analysis Population (ITT): n=610

	<b>CRT OFF (n=191)</b>	<b>CRT ON (n=419)</b>	<b>P-value</b>
<b>CCR WORSENE</b>	41	67	
<b>Percent with CCR WORSENE</b>	21%	16%	<b>0.10</b>

**Primary endpoint not met**

# Missing Data and Worst Case Analysis (REVERSE)

- Missing Data
  - 4 CRT ON patients
  - 0 CRT OFF patients
- Worst case (consider all missing as ‘worsened’)

	<b>CRT OFF (n=191)</b>	<b>CRT ON (n=419)</b>	<b>P-value</b>
<b>CCR WORSENERD</b>	41	71	
<b>Percent with CCR WORSENERD</b>	21%	17%	<b>0.18</b>

# Pre-specified US vs OUS Subgroup Analyses (REVERSE)

- If interaction between treatment group and US/OUS subgroup is significant:

Treatment effect **differs** in US and OUS patients

- Interaction of treatment and subgroup (US/OUS) is of concern (p-value=0.11)

	OUS		US	
	CRT OFF (n=83)	CRT ON (n=184)	CRT OFF (n=108)	CRT ON (n=235)
CCR WORSENE	22%	11%	<b>21%</b>	<b>20%</b>

# Components of the primary endpoint US vs OUS (REVERSE)

	OUS		US	
Clinical Composite Response Variable	CRT OFF (n=83)	CRT ON (n=184)	CRT OFF (n=108)	CRT ON (n=235)
<b>WORSENERD</b>	18 (22%)	20 (11%)	<b>23 (21%)</b>	<b>47 (20%)</b>
<b>Death</b>	3 (4%)	3 (2%)	<b>0 (0%)</b>	<b>6 (3%)</b>
Hospitalized for worsening HF	3 (4%)	4 (2%)	11 (10%)	10 (4%)
Crossover due to worsening HF	3 (4%)	0 (0%)	2 (2%)	1 (<1%)
<b>Moderately or Markedly Worse PGA and Worsened NYHA</b>	0 (0%)	1 (1%)	<b>0 (0%)</b>	<b>1 (&lt;1%)</b>
<b>Worsened NYHA</b>	9 (11%)	10 (5%)	<b>9 (8%)</b>	<b>28 (12%)</b>
Moderately or Markedly Worse Patient Global Assessment (PGA)	0 (0%)	2 (1%)	1 (1%)	1 (<1%)

# Discussion Items

1. REVERSE – Statistical design and major conclusions
  - Primary endpoint not met
  - Treatment may not be beneficial in US subjects
2. RAFT – Issues with design / conduct and implications
3. Validity of post-hoc analyses upon which proposed indication is based

# RAFT Study

- RAFT was an investigator-driven study
- Not conducted under IDE
  - IDE application was submitted and withdrawn
  - Conducted entirely OUS
- Decision to use study results as supporting evidence was post-hoc

# Concerns about RAFT study design

- Originally planned study: Group Sequential Trial
- Many **un-planned changes** to study design:
  - sample size
  - inclusion criteria
  - number and timing of interim looks
  - study power
  - minimum follow up duration
  - timing of interim analyses was unclear

**Statistical conclusions may not be valid as confirmatory evidence**



# Concerns about RAFT study conduct

- Nearly 25% of subjects unblinded
  - Unblinding of HF investigators could have been more prevalent
  - Blind could be broken by a request to cross-over treatment groups
- Missing data at baseline
  - 14% missing baseline 6-minute walk distance
  - Common reasons included time constraints
- Versions of CRF had check box only for NYHA class II

# Inadequately designed CRF's (RAFT)

## Excerpt from Baseline CRF

4.8 Supine Blood Pressure:    /    mmHg

4.9 Weight:     lbs. or     kg

4.10 Heart Failure Symptoms.....  Yes  No

If yes, check all that apply:

Dyspnea on Exertion  PND/orthopnea  Syncope

Fatigue  Angina  Other, specify

4.11 NYHA Classification: *Please choose one of the following*

NYHA Class II

# Concerns about RAFT study conduct

- Protocol deviations may have been under-reported in RAFT
  - Only 46 deviations related to inclusion/exclusion criteria
    - ❖ REVERSE: 121 deviations of inclusion/exclusion criteria
  - Only one reported deviation where subjects NYHA class was higher than allowed
  - Total number of protocol deviations reported in RAFT was less than a quarter of the deviations in REVERSE

# RAFT NYHA II Patients 'Sicker' than REVERSE NYHA II Patients

Baseline	REVERSE (n=503)	RAFT (n=1438)	P-value	"Sicker"
6-minute Hall Walk (m)	389.9 +/- 125.0	368.0 +/- 102.6	<.001	<b>RAFT</b>
Age (yrs)	62.9 +/- 11.0	65.9 +/- 9.4	<.001	<b>RAFT</b>
Ischemic	53% (266)	65% (941)	<.001	<b>RAFT</b>
Myocardial infarction	45% (228)	57% (826)	<.001	<b>RAFT</b>
Minnesota Living with HF	29.8 +/- 20.5	34.9 +/- 21.4	<.001	<b>RAFT</b>
Diabetes	24% (120)	33% (480)	<.001	<b>RAFT</b>
eGFR	73.4 +/- 24.4	61.6 +/- 20.7	<.001	<b>RAFT</b>
Coronary artery disease	49% (246)	56% (805)	0.007	<b>RAFT</b>
Previous CABG	28% (139)	33% (476)	0.026	<b>RAFT</b>
Prior HF Hospitalization	0	24%	-	<b>RAFT</b>

# RAFT Patients 'Sicker' than REVERSE

- Enrollment criteria in REVERSE were stricter
  - Patients with prior NYHA III/IV classification excluded in REVERSE (90 days prior)
  - Patients with prior hospitalization for HF excluded in REVERSE (90 days prior)
  - Baseline NYHA class to be confirmed by two qualified individuals in REVERSE

# Major difference in patient characteristics between RAFT and REVERSE

- In RAFT NYHA II patients, the time to first HF hospitalization or all-cause death was significantly prolonged by CRT-D

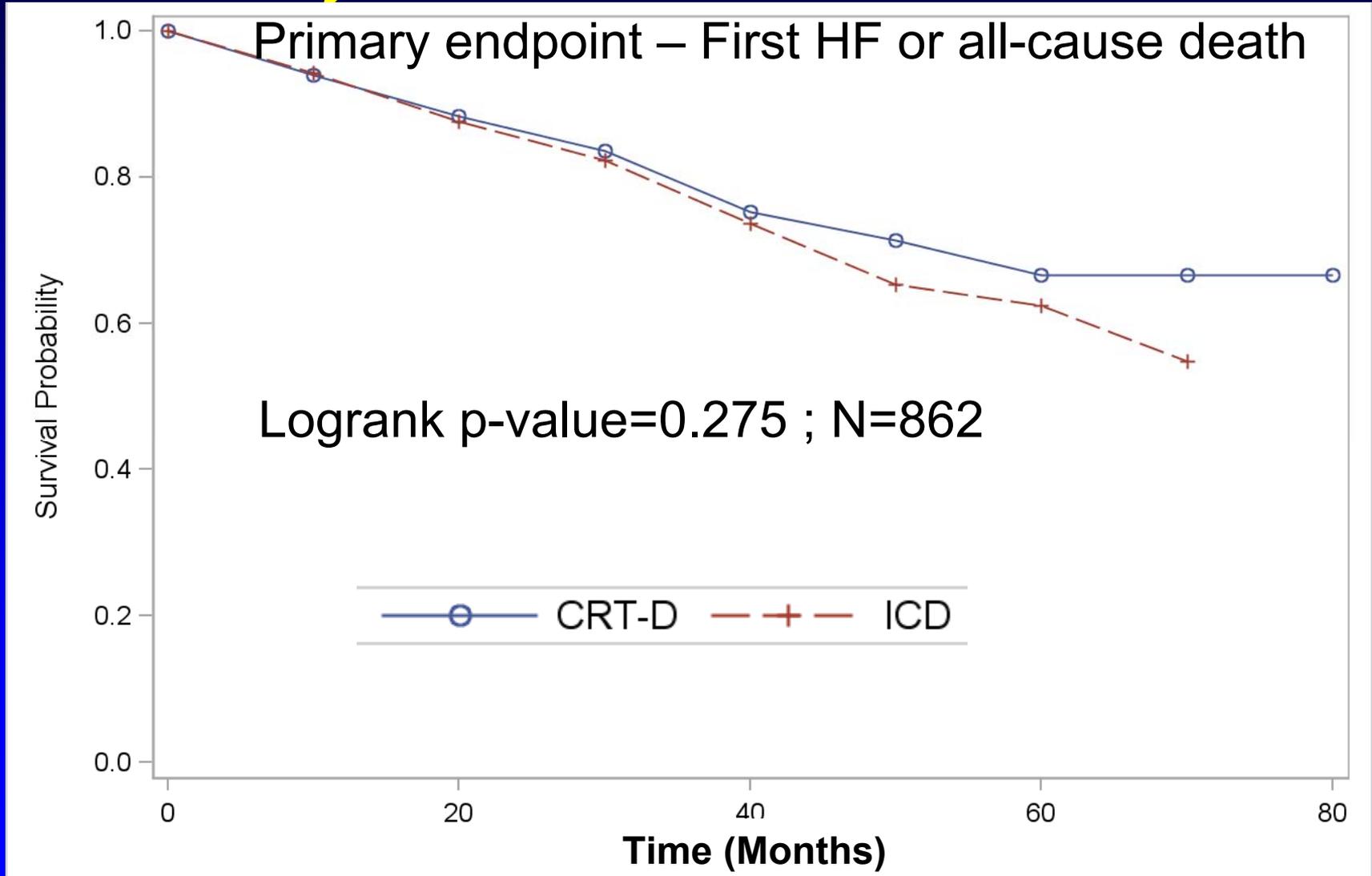
	REVERSE NYHA II (n=503)	RAFT NYHA II (n=1438)
Prior HF Hospitalization	0?	24%
Mean 6-minute Walk (m)	389.9	368.0



# FDA's Exploratory Analysis: What if we make RAFT NYHA II population similar to REVERSE?

- Make average 6-min walk test distance in RAFT similar to REVERSE
  - Exclude subjects with the shortest 6-min walk distances
  - Shortest 10% of 6 min walk distances in RAFT excluded
  - Mean 6-min walk for remaining subjects is 390 m
- Exclude 24% of NYHA II subjects with prior HF hospitalization
- Is there a treatment effect in RAFT when sicker patients are excluded?

# No treatment effect in 'less sick' NYHA class II subjects in RAFT



# Discussion Items

1. REVERSE – Statistical design and major conclusions
2. RAFT – Issues with design / conduct and implications
  - Results may be biased due to suboptimal design / conduct
  - No benefit of treatment when sicker NYHA II patients are excluded
3. Validity of post-hoc analyses upon which proposed indication is based



# Proposed population was selected post-hoc

- Proposed population based on post-hoc subgroup
  - ~30% of REVERSE study subjects in post-hoc subgroup (REVERSE-PPP)
  - 53% of RAFT subjects in post-hoc subgroup (RAFT-PPP)
- Neither REVERSE nor RAFT was designed for the proposed indication
  - proposed population based on post-hoc data exploration

**Post-hoc subgroup analyses are hypothesis  
generating and should be interpreted with  
caution**

# REVERSE-PPP does not support claims

- Reduction of HF hospitalization or all cause death
- Reduction of all cause death

	OUS		US	
	OFF (n=28)	ON (n=53)	OFF (n=36)	ON (n=72)
<b>Combined HF Hospitalization or All-Cause Death</b>	<b>3 (11%)</b>	<b>1 (2%)</b>	<b>4 (11%)</b>	<b>3 (4%)</b>
<b>All-Cause Death</b>	<b>2 (7%)</b>	<b>0 (0%)</b>	<b>0 (0%)</b>	<b>2 (3%)</b>

Only 11 HF hospitalization or death events in  
 REVERSE-PPP through 12 months

# RAFT-PPP subjects 'sicker' than REVERSE-PPP

Baseline	REVERSE (n=189)	RAFT (n=947)	P-value	"Sicker"
Age (yrs)	61.9 +/- 12.0	65.0 +/- 9.3	<.001	RAFT
Ischemic	41% (78)	61% (578)	<.001	RAFT
Myocardial infarction	34% (65)	53% (500)	<.001	RAFT
eGFR	73.6 +/- 24.8	63.4 +/- 21.1	<.001	RAFT
Minnesota Living with HF	29.3 +/- 20.0	34.6 +/- 21.3	0.002	RAFT
Previous CABG	19% (35)	30% (281)	0.002	RAFT
6-minute Hall Walk (m)	400.2 +/- 116.5	372.7 +/- 105.2	0.003	RAFT
Diabetes	22% (41)	32% (301)	0.005	RAFT
Coronary artery disease	41% (78)	51% (484)	0.014	RAFT
Prior HF Hospitalization	0	25%	-	RAFT

# Statistical Summary - REVERSE

- REVERSE study failed its primary endpoint.
- Effect of treatment is different for US and OUS subjects in REVERSE. Treatment may not be beneficial in US patients.



# Statistical Summary – RAFT

- Suboptimal study conduct jeopardizes the validity of RAFT.
  - Revisions to the protocol
  - Inadequate case report forms
  - Under-reporting of protocol deviations
- RAFT may have enrolled sicker subjects than is apparent from NYHA functional class. Results in RAFT appear to be driven by ‘sicker’ subjects.



# Statistical Summary

## Post-Hoc Subgroup

- Proposed indication based on post-hoc subgroup
  - Post-hoc subgroup analyses are hypothesis generating
- Proposed claims not supported by the totality of data
  - Limited number of death and HF hospitalization events in REVERSE-PPP



**Proposed Expansion of Indications  
for Medtronic's CRT-D Devices  
based on  
REVERSE and RAFT Studies**

**FDA Review of P010031 / S232**

**Shaokui Wei, MD, MPH  
Division of Epidemiology  
Office of Surveillance and Biometrics  
Food and Drug Administration  
December 7, 2011**



## Reminder

- Discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective
- Plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval
- Premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a **reasonable assurance of safety and effectiveness** and an appropriate risk/benefit balance



# Need for 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

# Post-Approval Study Components

- Fundamental study question or hypothesis
- Well-specified study population and study design
- Safety endpoints and methods of assessment
- Acute and chronic effectiveness endpoints and methods of assessment
- Duration of follow-up



# Important Postmarket Issues

Long-term (5-year) performance of the device in:

- more general, real-world, US patient population;
  - premarket datasets comprised of substantial OUS proportion
- more diverse patient population, including sufficient sampling of females
  - premarket analyses not powered to examine LBBB and gender sub-group performance

# Overview of Sponsor's Proposal

Study Design	<p>A single-arm observational study to estimate 5-year survival probability by utilizing patients enrolled in the NCDR ® ICD Registry</p> <p>No hypothesis and comparison group</p>
Endpoints	<ul style="list-style-type: none"> <li>• <b><u>Primary endpoints</u></b>: 5 year all-cause mortality</li> <li>• <b><u>Secondary endpoints</u></b>: primary endpoint stratified by gender at 5 years</li> </ul>
Population	1500 patients from the NCDR ® ICD Registry
Follow-up	Patient mortality data will be collected via the Social Security Death Index (SSDI)
Statistical Analysis	Kaplan-Meier estimate of 5 year survival with 2-sided 95% confidence intervals

# Sample Size Justification

- 1500 patients (~345 women)
- 95% confidence interval width
  - 4.5% overall
  - 10% for women
- Assuming:
  - 25% 5-year cumulative mortality rate
  - 5% total attrition accounting for lost-to-follow-ups

# Assessment of Sponsor's Proposal

1. No study hypothesis or comparison group making it difficult to determine whether CRT-D truly provides a long-term beneficial effect.
2. Long-term all cause mortality evaluated via SSDI, but heart failure endpoints not assessed.
3. The small proposed proportion of females (25-30%, 345), will not provide enough precision to assess effectiveness by gender
4. NCDR ICD Registry contains procedural and in-hospital safety data, yet safety is not assessed in the proposed PAS. This makes it difficult to evaluate the long-term risk-benefit ratio.

# Beltway Briefings for Social Security Administration –November 2011

*As Beltway Briefings, November 2011,* General Counsel to the Social Security Administration (SSA) has determined that it is illegal for the SSA to “re-disclose” the death records that it receives from individual states. As a result, SSA has cut off researchers’ access to the Social Security Death Master File (SSDMF), a database of death records containing information on all persons assigned a Social Security number who died after 1962 and whose death was reported to the SSA.

<http://www.sts.org/news/social-security-administration-cuts-access-death-master-file>



# FDA's Summary

# REVERSE: Summary of Concerns

## Pivotal Study Data

- Failed primary endpoint
- Differences between US and OUS patient characteristics and results
- Difficulty interpreting secondary analyses
- Limitations in the evaluation of the Clinical Composite Response endpoint

# RAFT: Summary of Concerns

## Supporting Study Data

- Higher than expected mortality rate compared to similar CRT trials
- Multiple revisions to the inclusion criteria and statistical analysis plans
- Limitations of previous hospitalization data and baseline NYHA Class data at enrollment
- High rate of unblinding and crossovers
- Limited monitoring and collection of protocol deviations

# Overall: Summary of Concerns

## Both Studies

- Post-hoc analyses of the proposed patient population
- Baseline doses and changes in doses of heart failure medications
- Totality of data from both studies does not support the proposed claims

Questions?