

# What have we learned from CRT trials in mild heart failure?

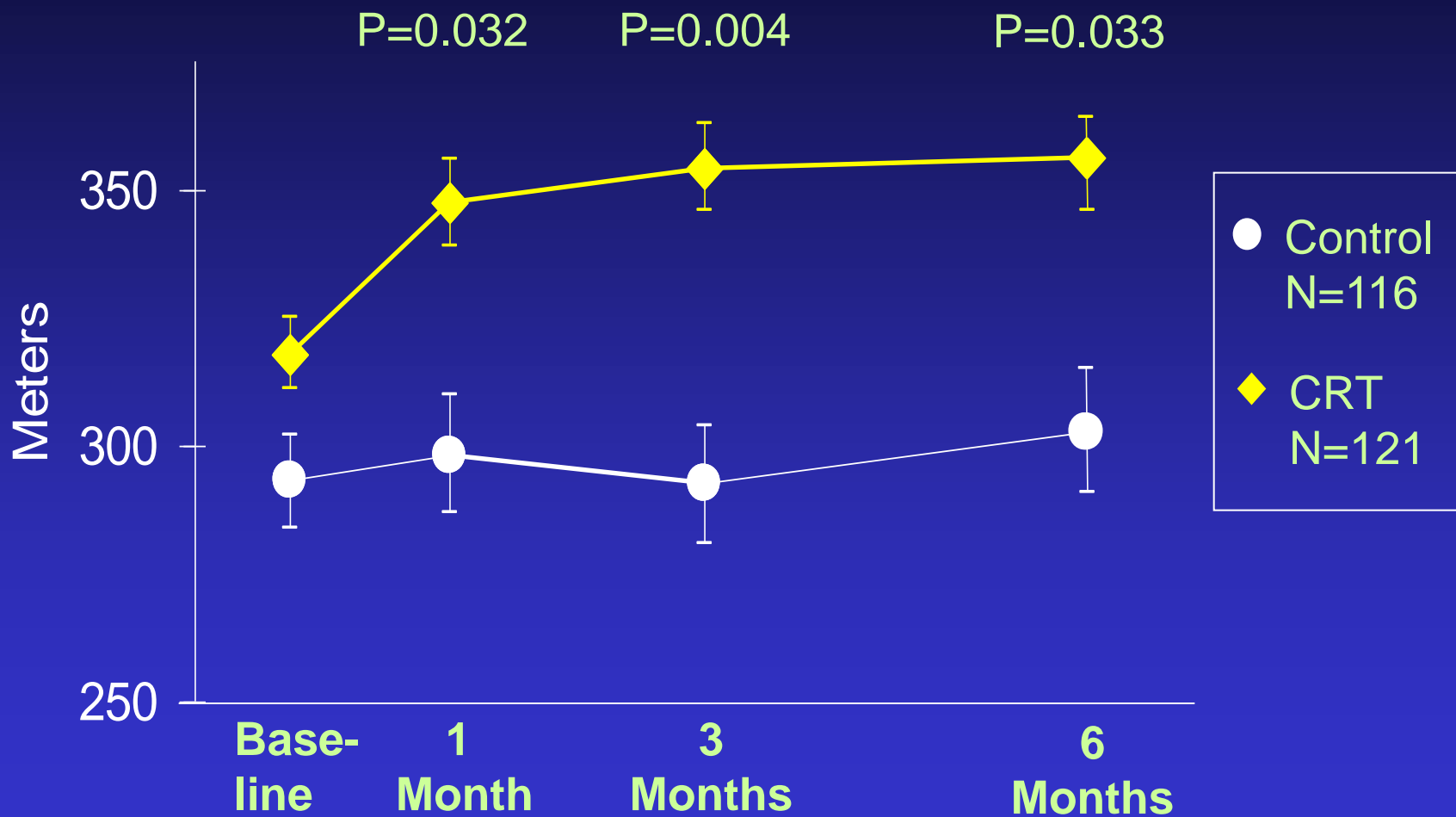
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**Charleston, SC**

Disclosures: Consultant and Clinical Trials-  
Boston Scientific, Cameron Health, Medtronic,  
Sorin, St. Jude

# Cardiac Resynchronization Therapy: Weight of Evidence

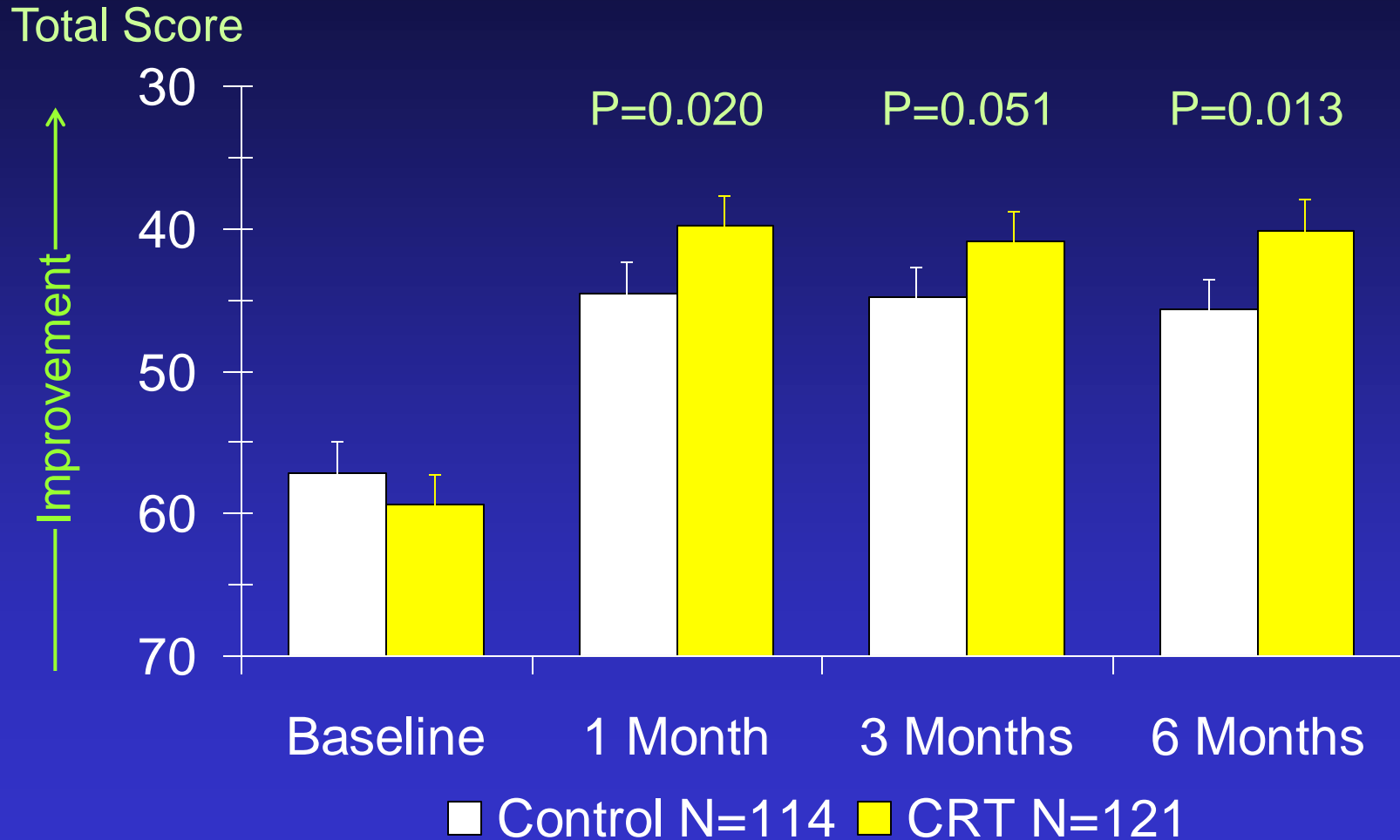
- >5,000 patients evaluated in randomized controlled trials of advanced HF subjects
- Consistent improvement in quality of life, functional status, and exercise capacity
- Strong evidence of changes in LV structure
  - ↓ LV volumes and dimensions
  - ↑ LVEF
  - ↓ Mitral regurgitation
- Reduction in HF and all-cause morbidity and mortality

# 6-Minute Hall Walk

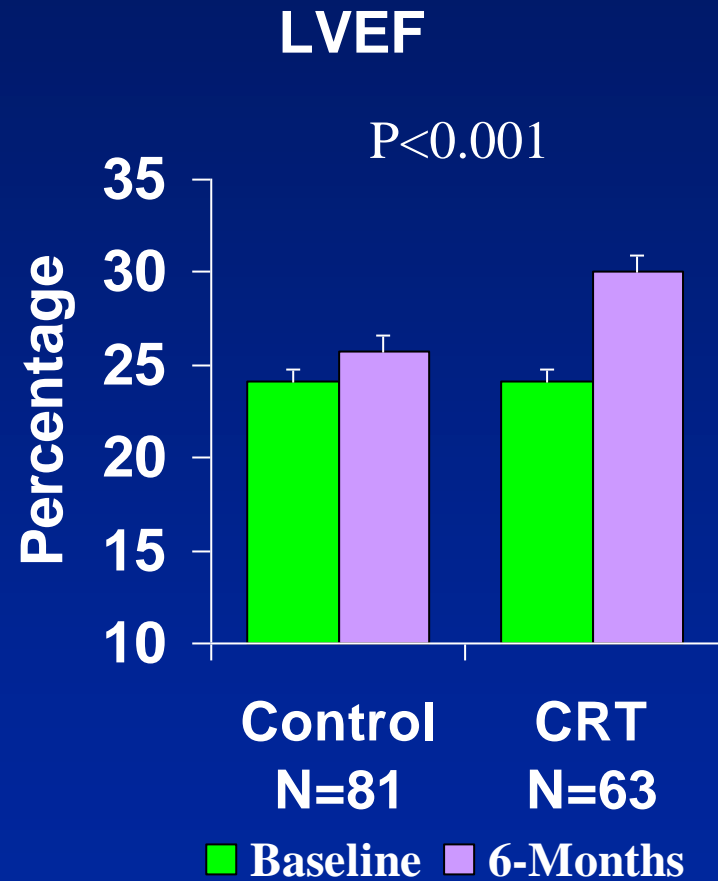
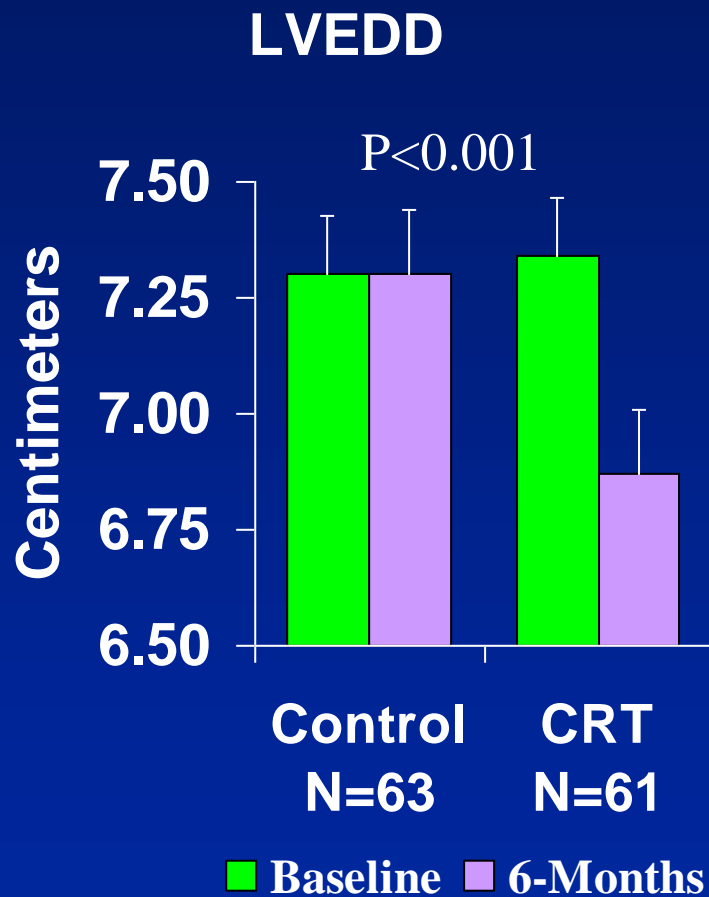


# Quality of Life

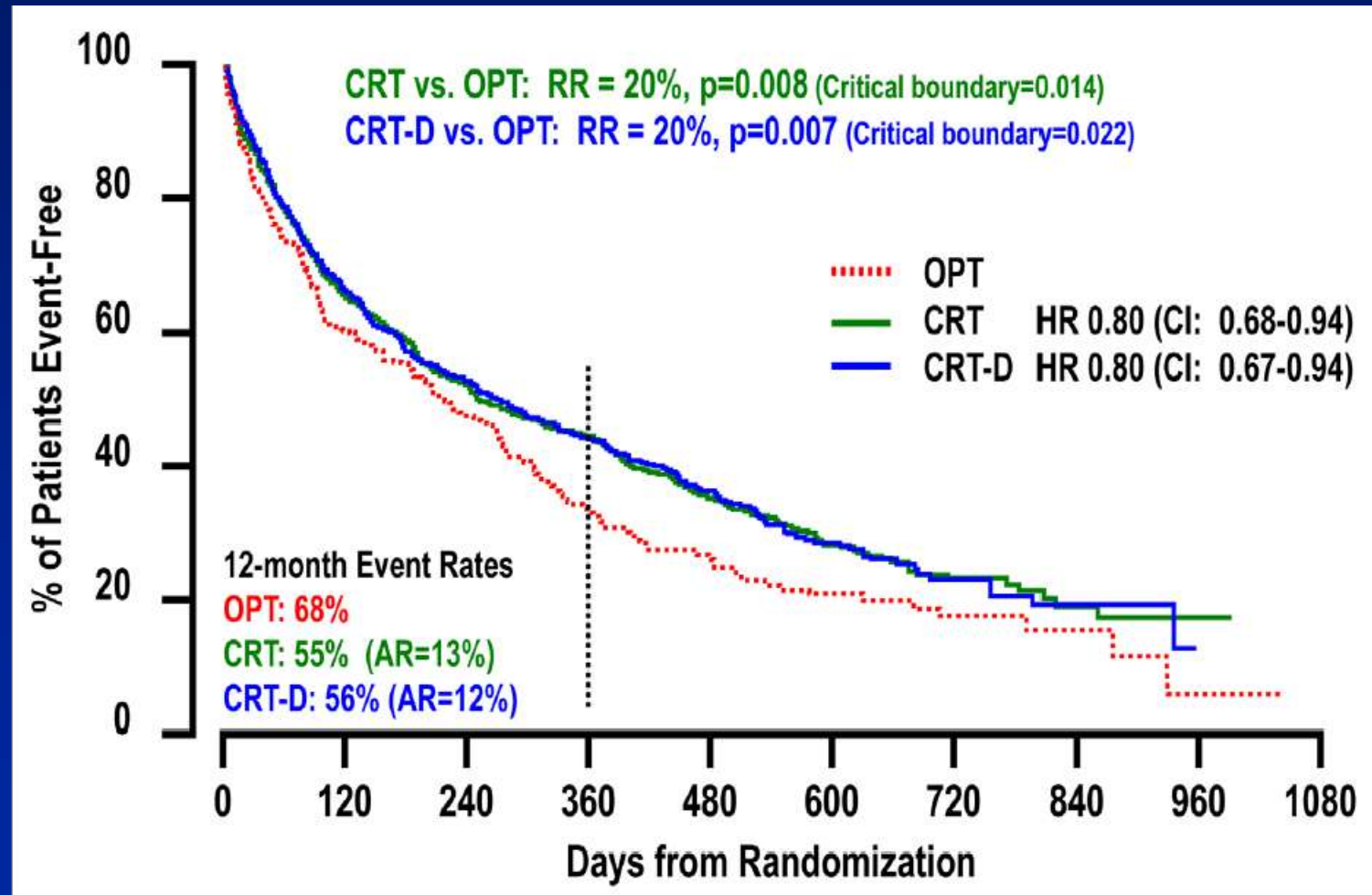
## Minnesota Living With Heart Failure Score



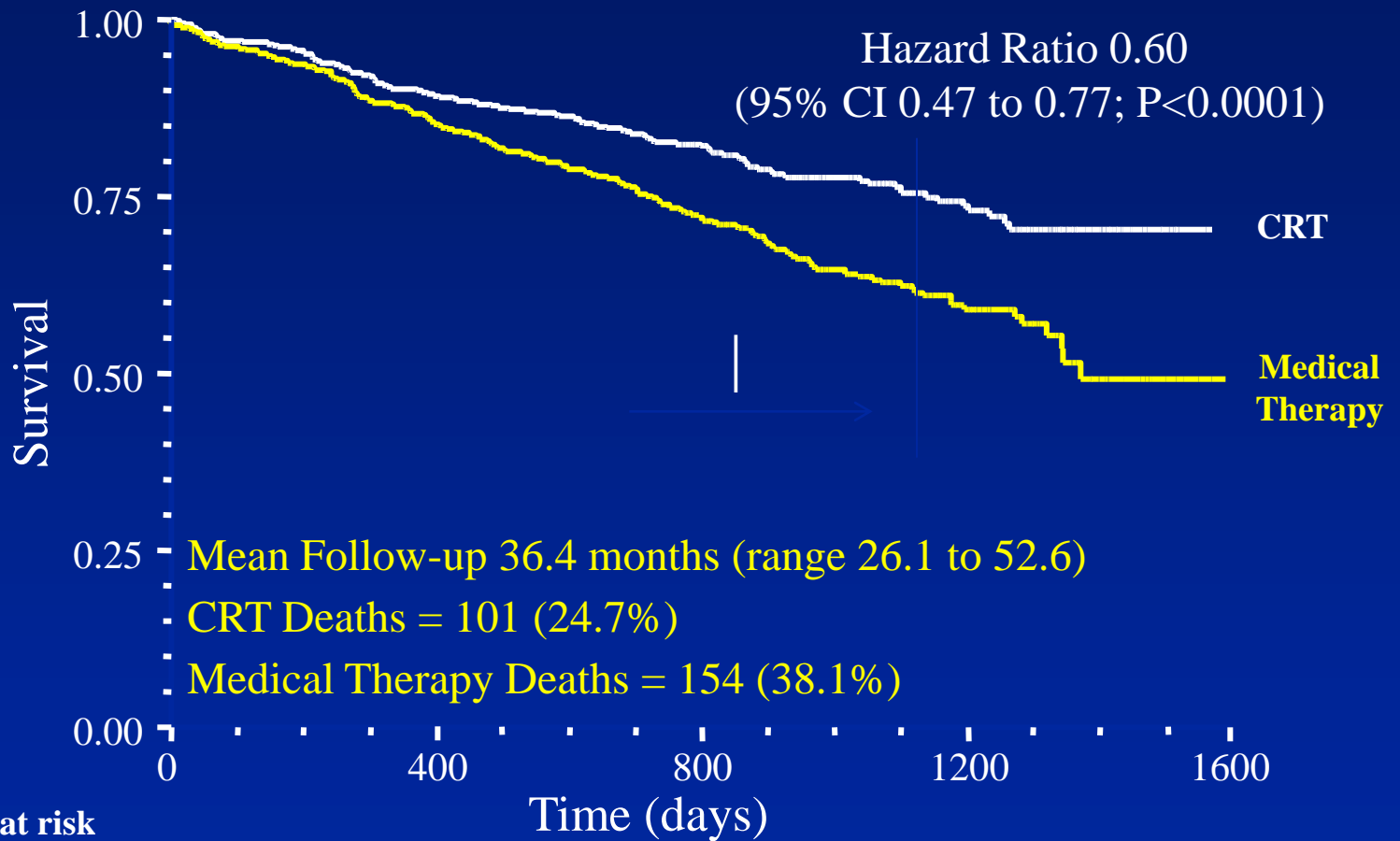
# Echocardiographic Parameters



# COMPANION: Primary Endpoint Death or Any Hospitalization



# CARE-HF



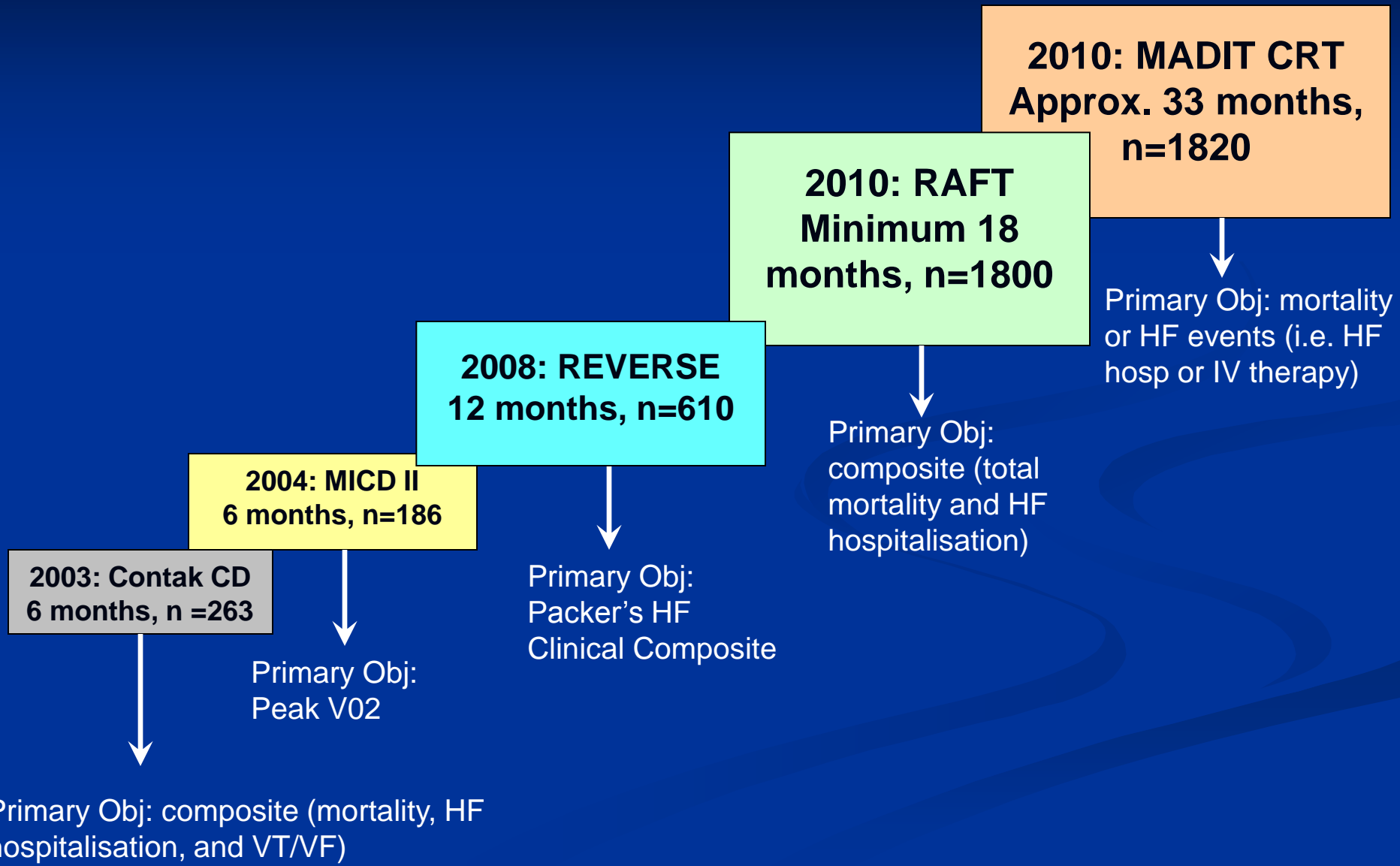
Number at risk

CRT	409	383	358	338	209	85	9
Medical therapy	404	372	331	298	178	63	6

# Early Intervention of CRT in CHF

- ◆ Most therapies in cardiology have evolved from secondary prevention to primary prevention
- ◆ We do not wait for an MI before treating hyperlipidemia
- ◆ We do not wait for a cardiac arrest before implanting an ICD
- ◆ Patients with heart disease who progress from asymptomatic stage B to symptomatic stage C heart failure have a 5x increased risk of death in 5 years
- ◆ Why wait for NYHA III CHF before implanting a CRT?

# Landscape of CRT Trials in NYHA I, II



# REVERSE Study Design

**Baseline**

NYHA Class II or I (previously symptomatic), NSR, QRS  $\geq$  120 ms, LVEF  $\leq$  40%, LVEDD  $\geq$  55 mm, without bradycardia, with or without ICD indication, on optimal medical therapy

**All receive implant attempt**

**Successful CRT Implant**

**1:2 randomization**

**Randomized**

***CRT OFF***  
**(OMT or OMT+ICD)**

***CRT ON***  
**(CRT+OMT or CRT+OMT+ICD)**

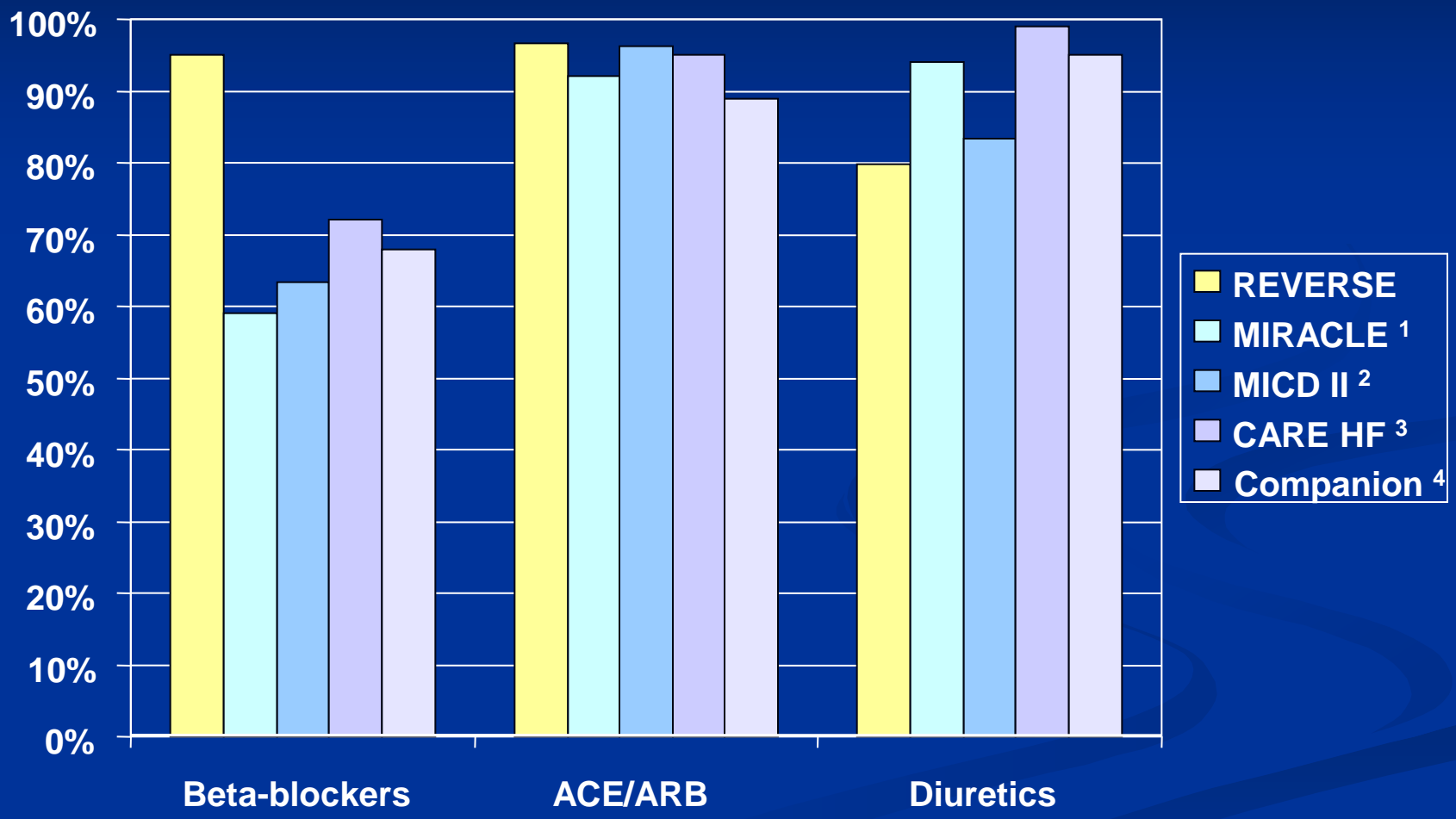
**1, 3, 6, 12 Months**

*Patients and clinicians  
managing HF are blinded*

**1, 3, 6, 12 Months**

**At 1 Year in US and 2 yrs in Europe, all patients have CRT ON  
continued yearly follow-up over 5 yrs**

# Comparison Between Trials (Medication)



1. NEJM 2002; 236:1845-53  
2. Circ. 2004;110:2864-68

3. NEJM 2005; 352:1539-49  
4. NEJM 2004; 350:2140-2150

# Comparison Between Trials (LV Function)

	<b>REVERSE NYHA I-II</b>	<b>Contak CD<sup>1</sup> NYHA I-II</b>	<b>MICD II <sup>2</sup></b>	<b>Contak CD<sup>1</sup> NYHA III-IV</b>	<b>MIRACLE<sup>3</sup></b>	<b>MICD<sup>4</sup></b>	<b>CARE HF<sup>5</sup></b>
LVEF (%)	<b>27</b>	<b>22</b>	<b>24</b>	<b>21</b>	<b>24</b>	<b>24</b>	<b>26</b>
LVEDD (mm)	<b>69</b>	<b>70</b>	<b>75</b>	<b>72</b>	<b>74</b>	<b>76</b>	<b>72</b>
LVESD (mm)	<b>58</b>	<b>58</b>	<b>65</b>	<b>60</b>	<b>64</b>	<b>67</b>	
LVEDV (mL)	<b>269</b>		<b>335</b>		<b>295</b>	<b>317</b>	
LVESV (mL)	<b>199</b>		<b>259</b>		<b>228</b>	<b>244</b>	
	<b>NYHA I-II</b>			<b>NYHA III-IV</b>			

1. JACC 2003; 42 1454-59  
2. Circ. 2004;110:2864-68

3. Circulation 2003;107:1985-1990  
4. JAMA 2003;289:2685-94

5. NEJM 2005; 352:1539-49

# Comparison Between Trials

	REVERSE	MIRACLE <sup>1</sup>	MICD II <sup>2</sup>	CARE HF <sup>3</sup>	Companion <sup>4</sup>
MN LWHF	27.6	59	40.7	45	45
6MHW	395.2	298	370	Na	258
QRS	153.3	166	166	165	160
NYHA by Investigator	I 18%	I 0%	I 0%	I 0%	I 0%
	II 82%	II 0%	II 100%	II 0%	II 0%
		III 90%		III 94%	III 86%
		IV 10%		IV 6%	IV 14%

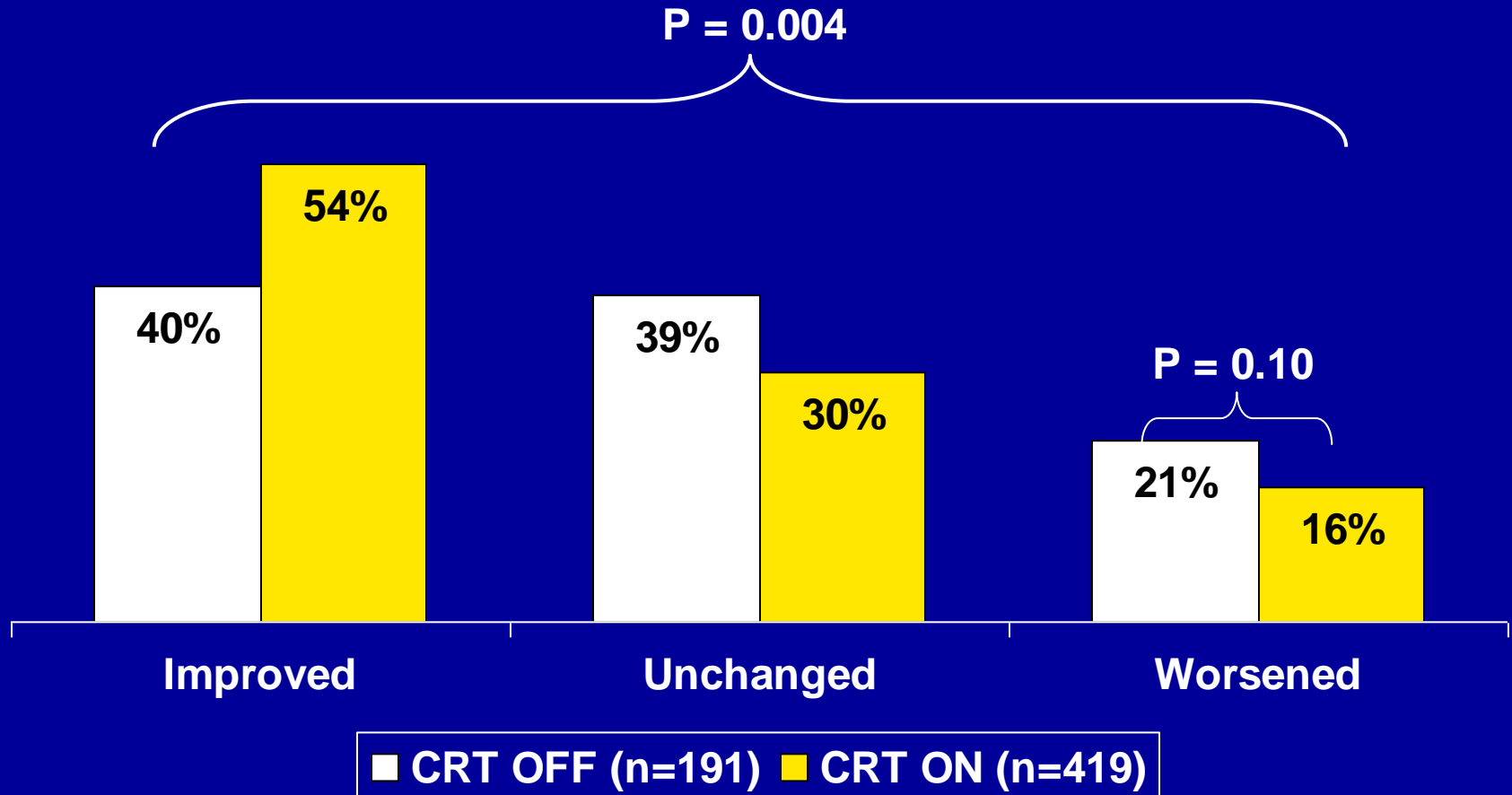
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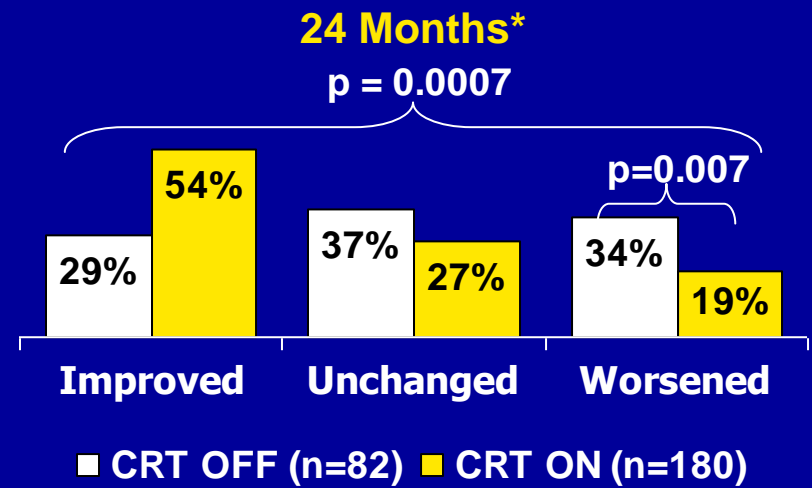
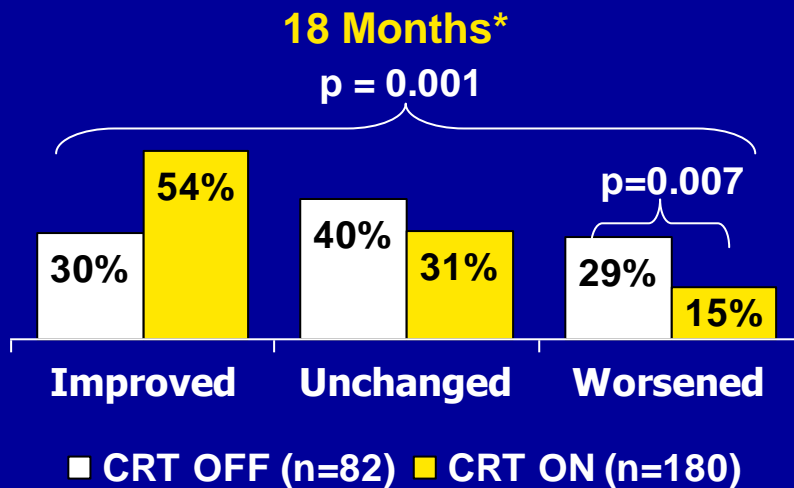
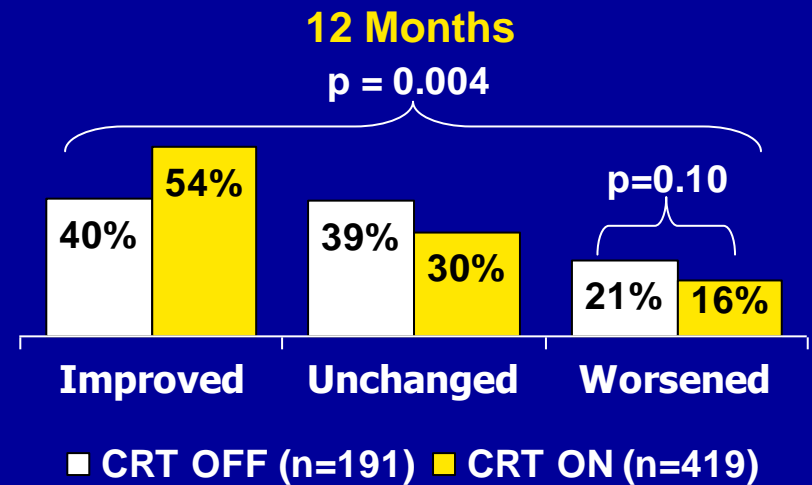
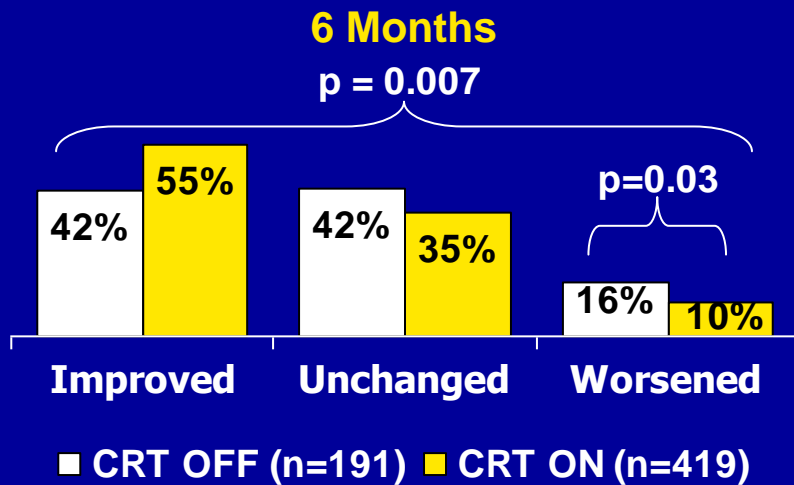
# *Primary End Point*

- HF Clinical Composite Response, comparing the proportion of patients worsened in CRT OFF vs. CRT ON groups
  - All-cause mortality
  - HF hospitalizations
  - Crossover due to worsening HF
  - NYHA class
  - Patient global assessment

# REVERSE: Full Distribution of Clinical Composite Response Improved with CRT

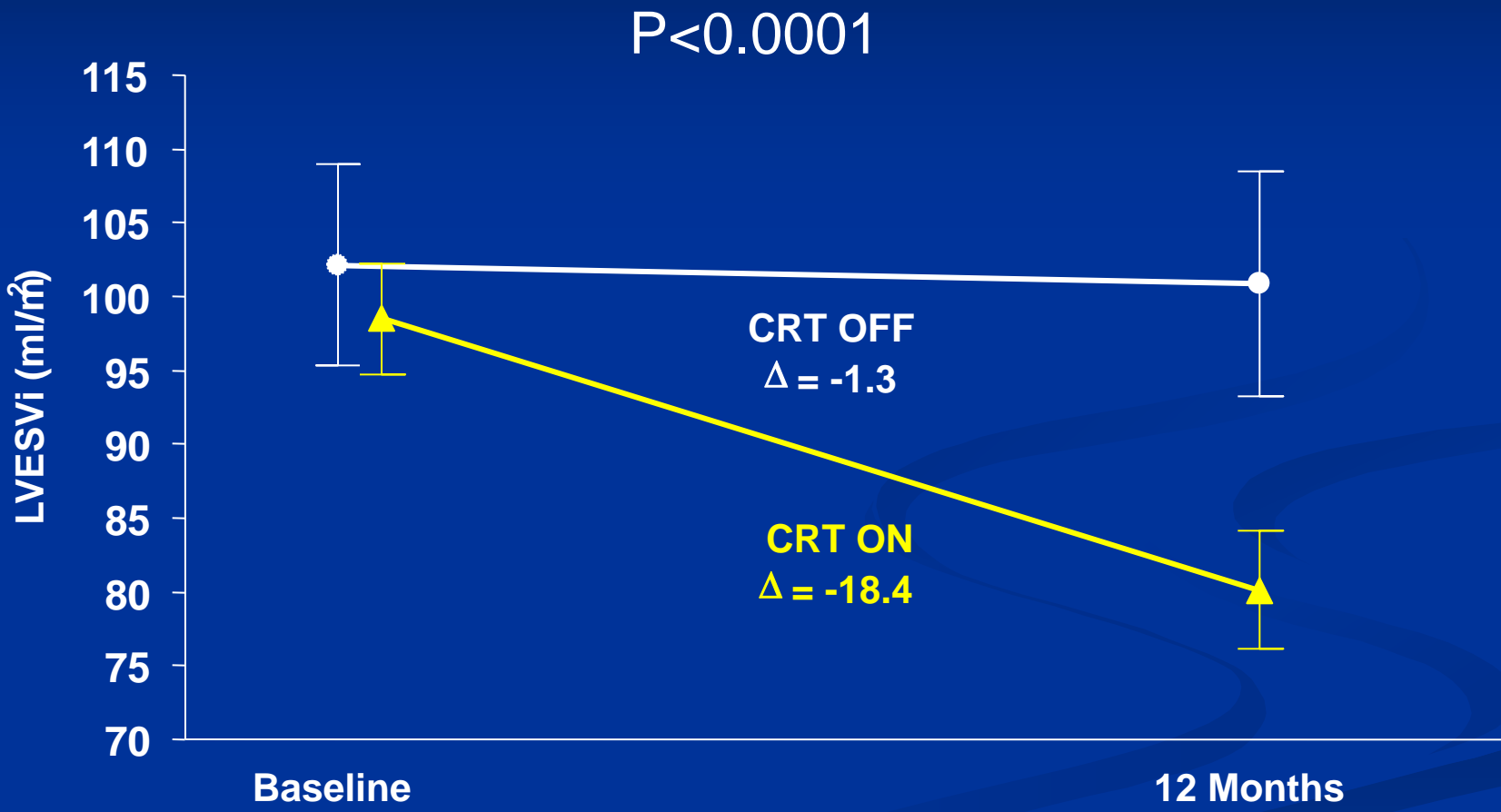


# REVERSE: Consistent Benefit in Clinical Composite Response Over Time

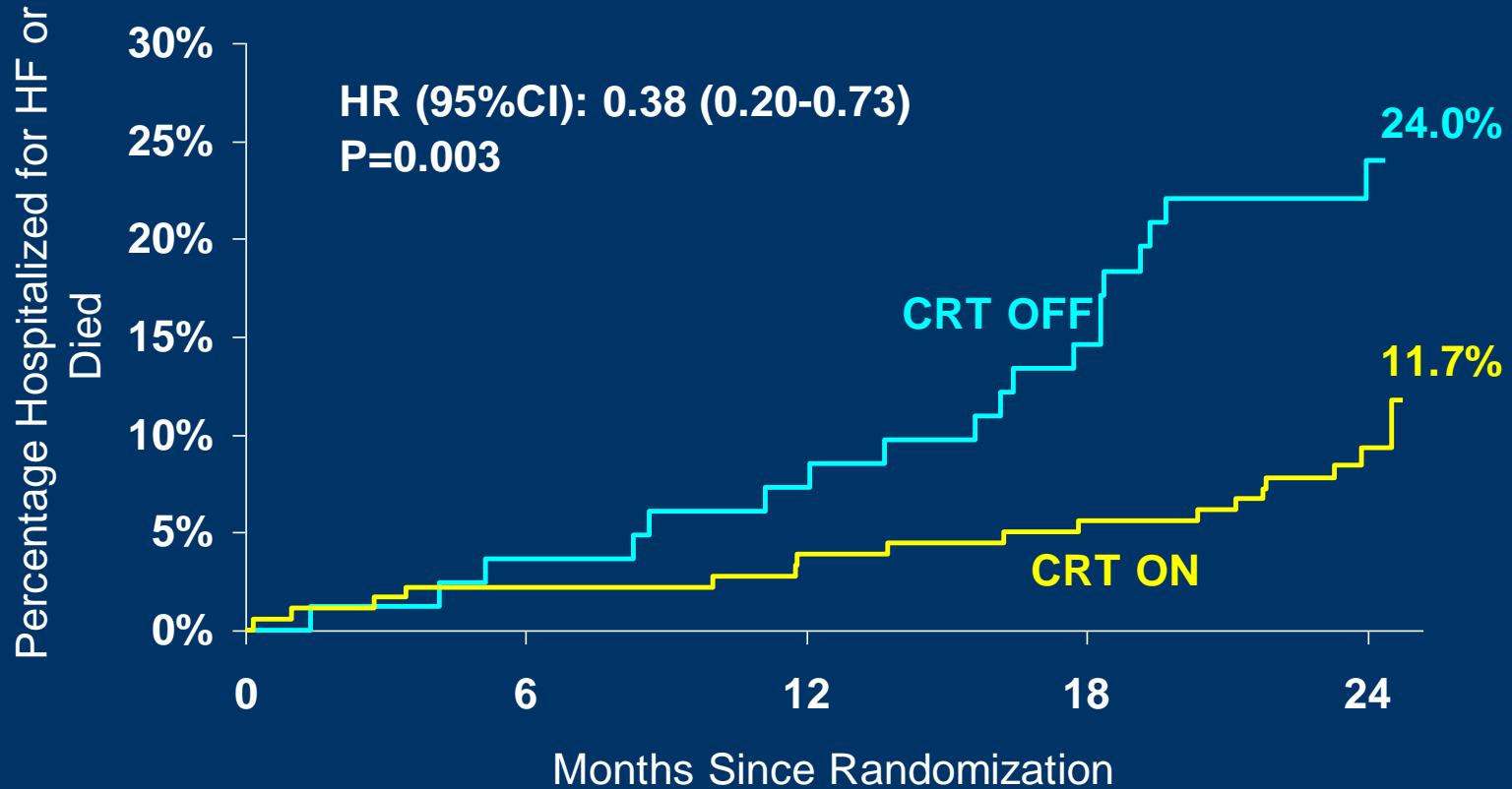


\* Europe only

# Powered Secondary End Point: LVESVi (ml/m<sup>2</sup>)



# Time to First HF Hospitalization or Death



Number at Risk

CRT OFF	82	79	76	70	39
CRT ON	180	176	173	168	77

# MADIT-CRT

- Ischemic heart disease (NYHA Class I or II) or non-ischemic heart disease (NYHA Class II) for at least three months prior to entry
- Optimal pharmacologic therapy
  - Beta blockers, ACE/ARB, and statins (ischemic patients) unless not tolerated or contraindicated
- Left ventricular ejection fraction  $\leq 30\%$
- QRS duration  $\geq 130$  ms
- Sinus rhythm

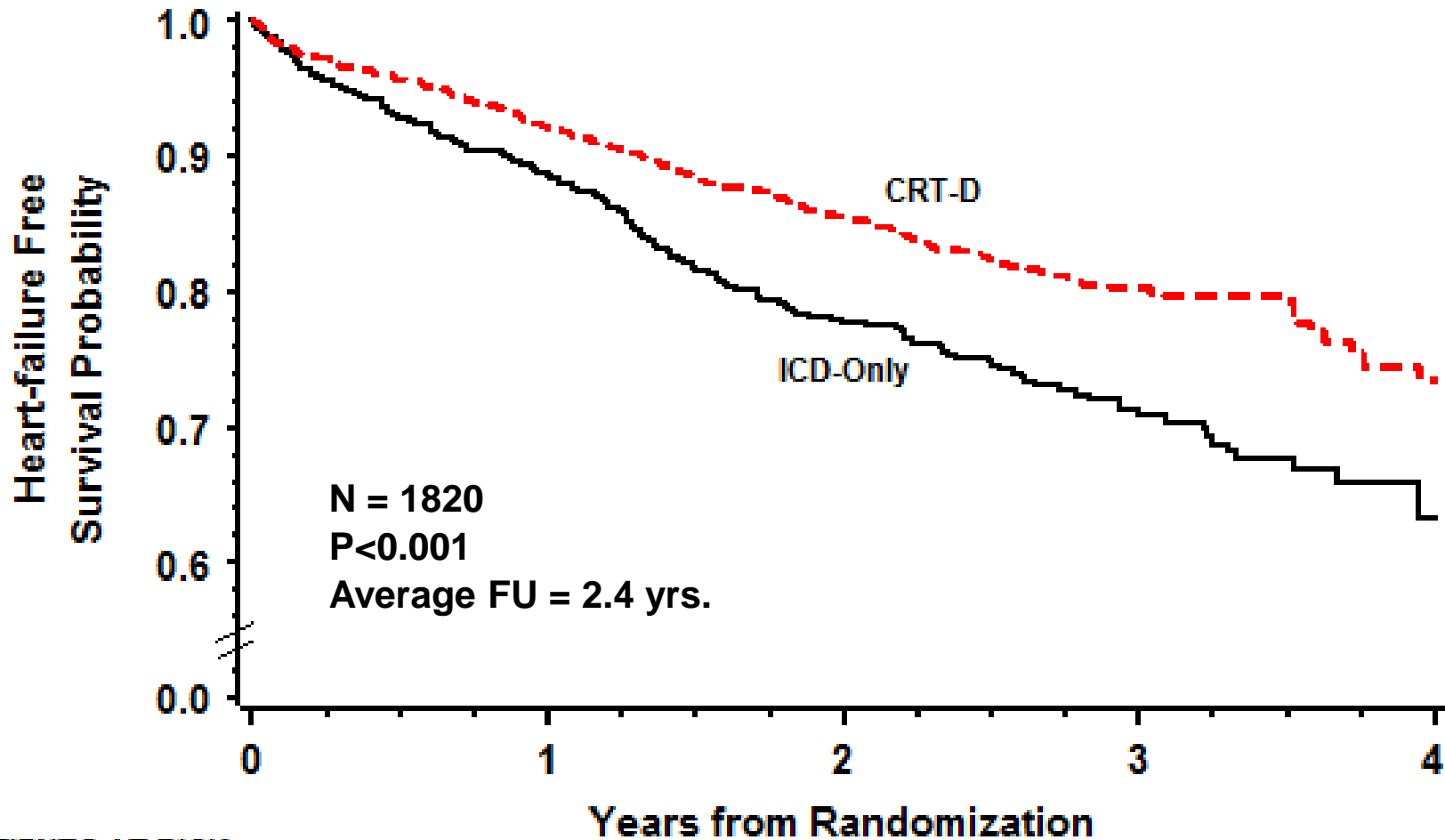
# MADIT-CRT: Primary End Point

## First Occurrence

1. All-cause Mortality, or
2. Heart-failure Event\*: S & S of HF with response to Rx involving
  - a) iv decongestive therapy in an “out-patient” setting; or
  - b) augmented decongestive iv or oral therapy during in-hospital stay

\*Adjudicated by Independent Blinded End-point Review Committees

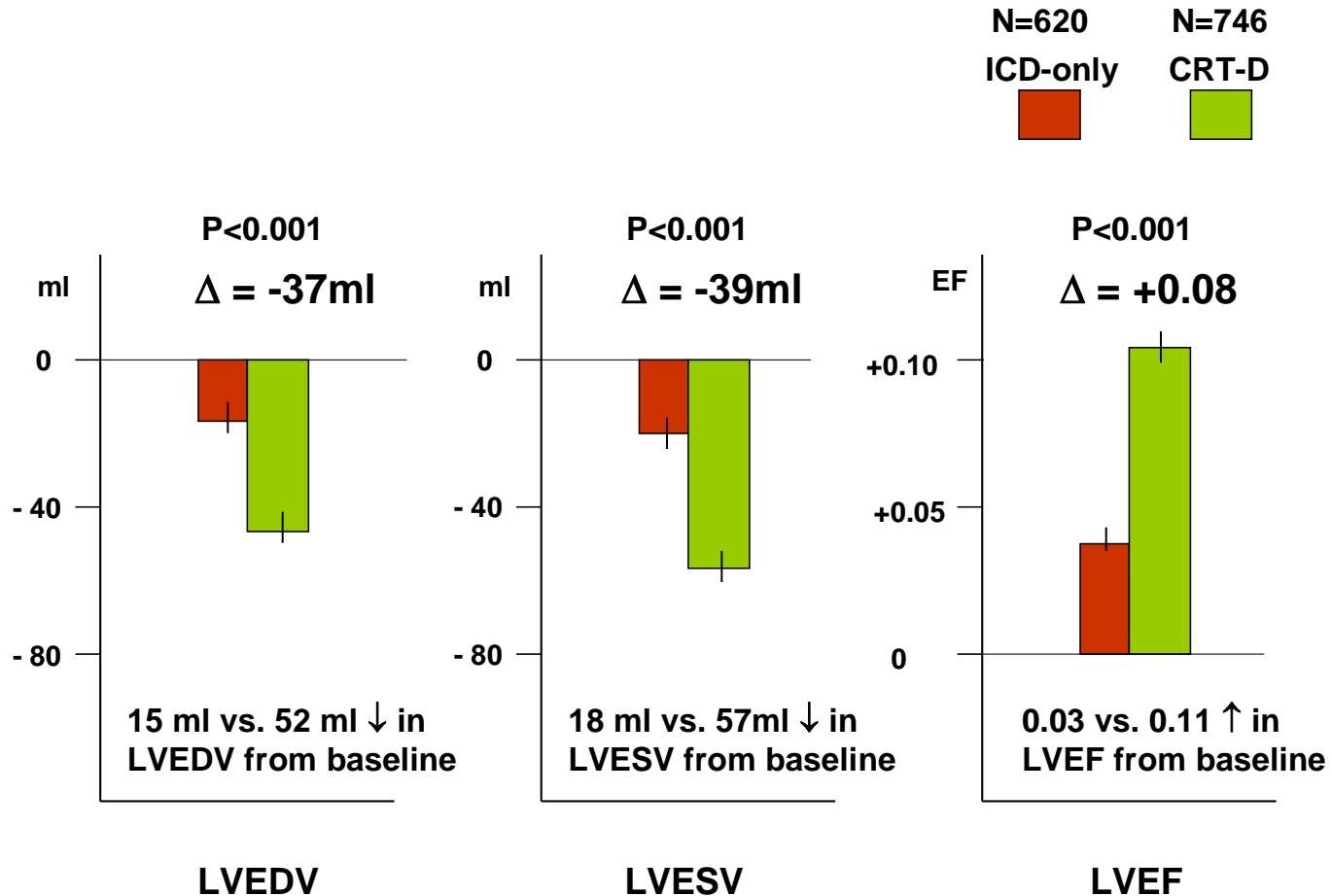
# MADIT-CRT: Kaplan-Meier Estimate of Heart-failure Free Survival Probability



## PATIENTS AT RISK

ICD-Only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT-D	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

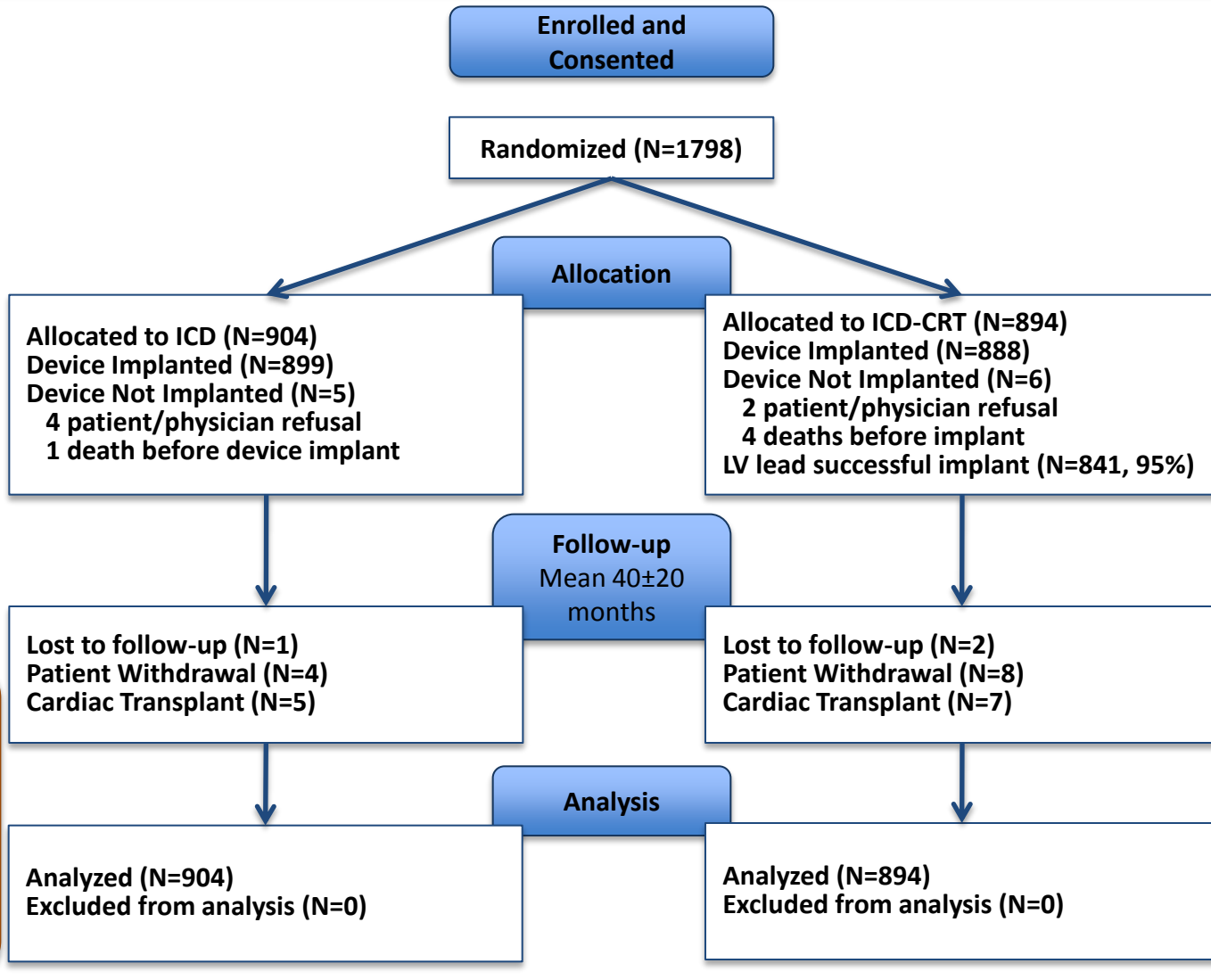
# Mean Changes in Echo LV Volumes and EF from Baseline to 1-year by Treatment Group



**CRT-D associated with significant reduction in heart size and improvement in heart function.**



# Consort Flow Diagram

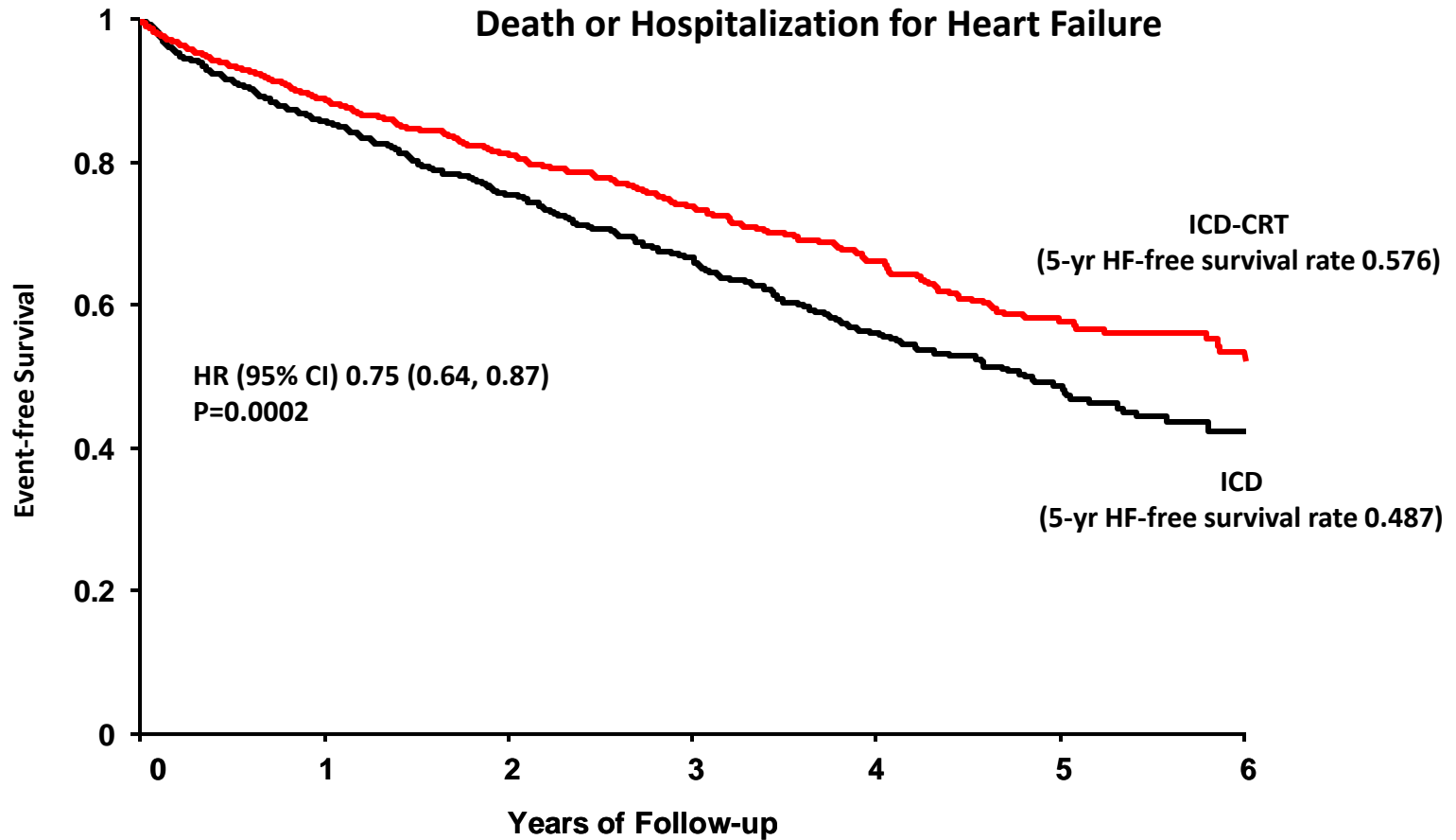


Cross-over  
ICD to ICD/CRT  
36 (4.0%)  
before  
reaching 1°  
endpoint  
60 (6.6%)  
after  
reaching 1°  
endpoint

Cross-over  
ICD/CRT to  
ICD  
47 (5.3%)  
failed LV lead  
implant  
6 (0.7%)  
non-  
functioning LV  
lead



# Kaplan-Meier Estimates of the Primary Outcome

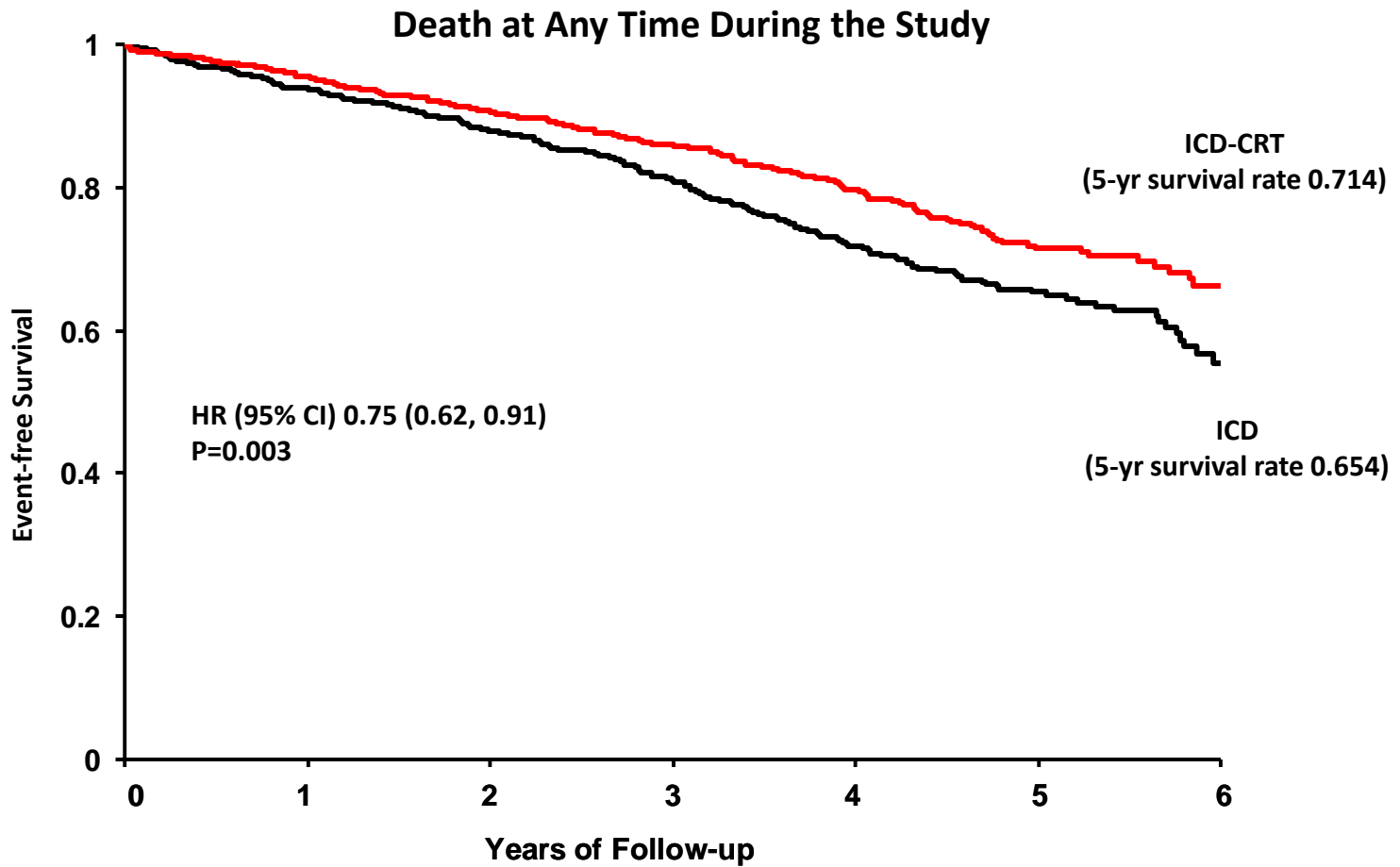


**No. at Risk**

ICD/CRT	894	790	615	429	278	130	41
ICD	904	770	572	384	214	101	19



# Kaplan-Meier Estimates of All cause Mortality



**No. at Risk**

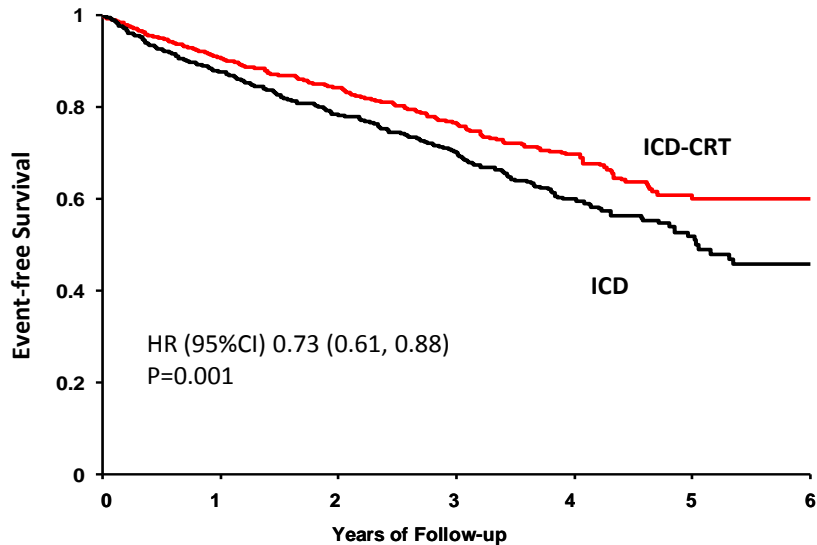
ICD/CRT	894	849	685	502	333	167	53
ICD	904	841	670	482	289	149	35



# Kaplan-Meier Estimates of the Primary Outcome and Death by NYHA Class

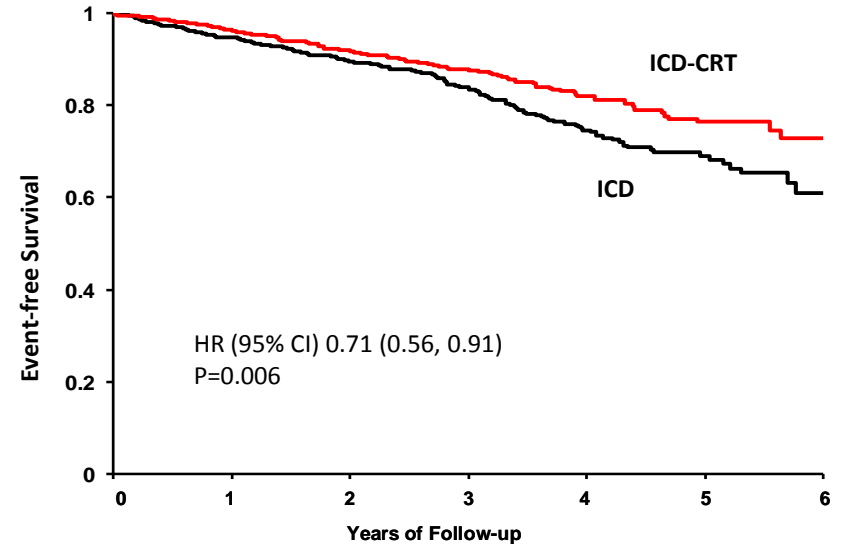
## NYHA Class II

Death or Hospitalization for Heart Failure



No. at Risk	0	1	2	3	4	5	6
ICD/CRT	708	640	488	315	181	70	15
ICD	730	638	465	299	146	57	6

Death from any cause



No. at Risk	0	1	2	3	4	5	6
ICD/CRT	708	679	530	361	206	89	20
ICD	730	687	533	366	189	83	13

# What Else Have We Learned from CRT in Mild Heart Failure Trials?

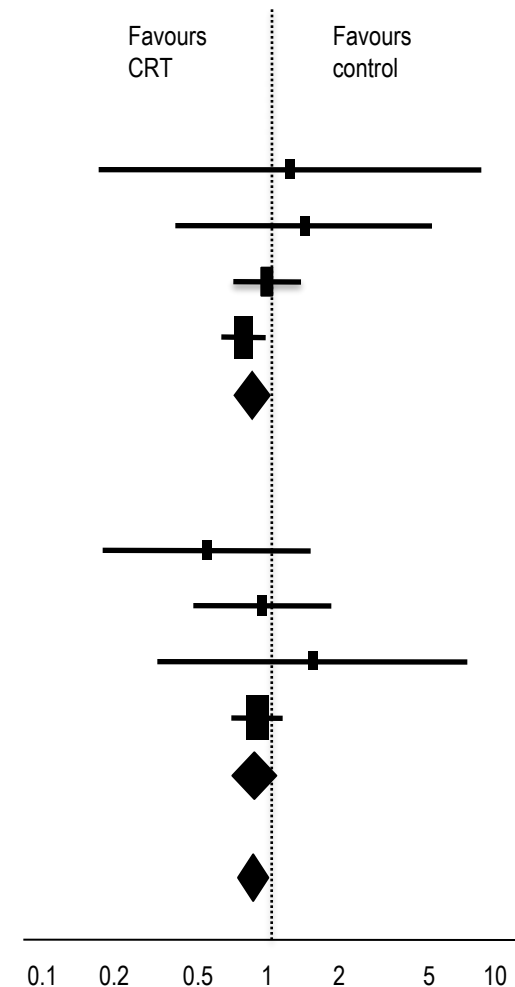
- ◆ Magnitude of Response
- ◆ Clinical Predictors of Response
- ◆ Impact of Reverse Remodeling
- ◆ Importance of LV lead position



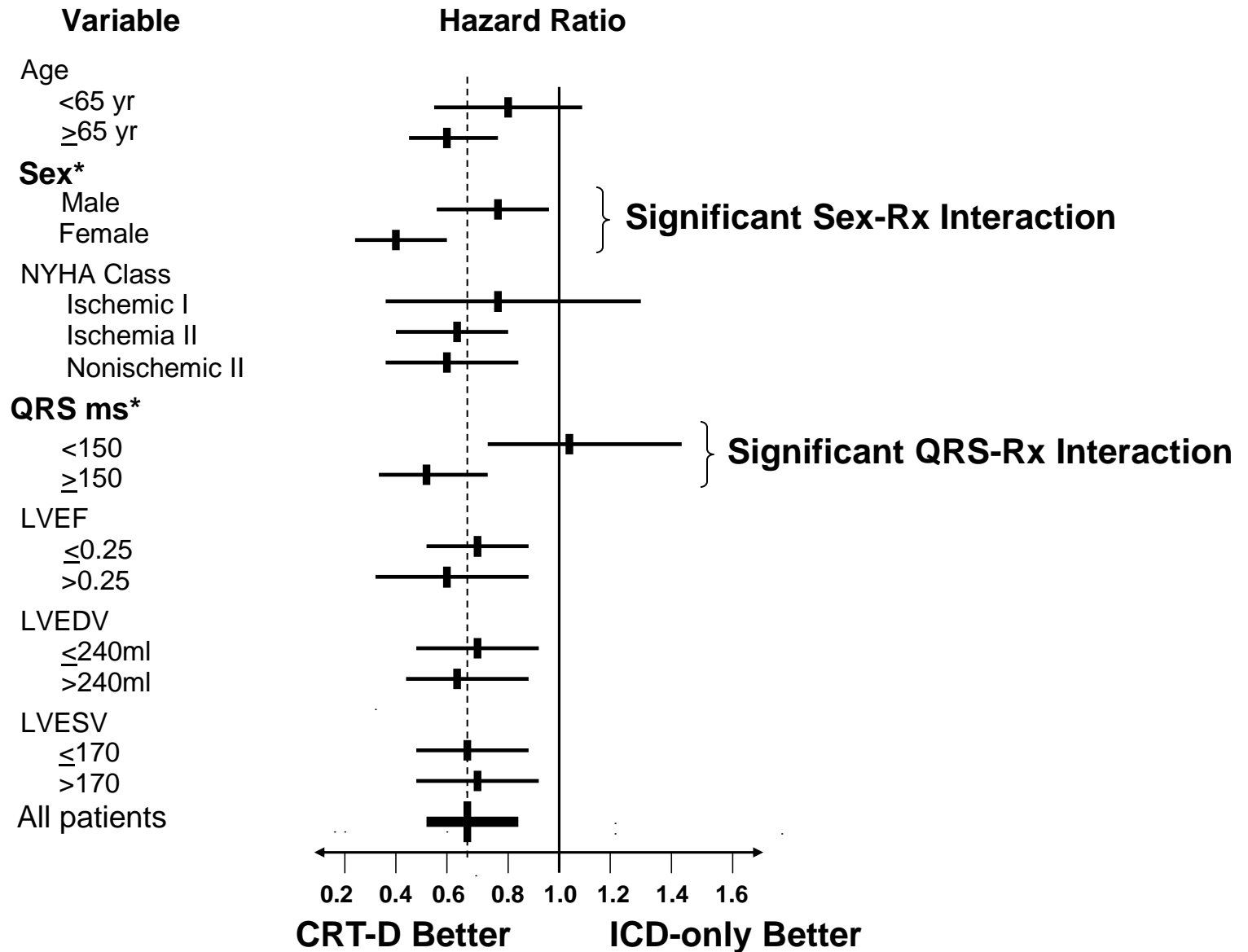
# Meta-analysis of RCT: All cause Mortality

## Effect of CRT added to ICD by NYHA Class

Study	Study group , n/N		RR (95% CI)
	ICD-CRT	ICD	
<b>NYHA Class I and II</b>			
MIRACLE ICD II 2004	2/85	2/101	1.19 (0.17, 8.26)
REVERSE (ICD) 2008	9/419	3/191	1.37 (0.37, 4.99)
MADIT-CRT 2009	74/1089	53/731	0.94 (0.67, 1.32)
RAFT (Class II)	110/708	154/730	0.74 (0.59, 0.92)
Subtotal	195/2301	212/1753	0.80 (0.67, 0.96)
<b>NYHA Class III and IV</b>			
Lozano 2000	5/109	10/113	0.52 (0.18, 1.47)
MIRACLE ICD 2003	14/187	15/182	0.91 (0.45, 1.83)
RHYTHM ICD 2004	6/119	2/60	1.51 (0.31, 7.27)
RAFT (Class III) 2010	76/186	82/174	0.87 (0.69, 1.10)
Subtotal	101/601	109/529	0.86 (0.69, 1.07)
Total	296/2902	321/2282	0.83 (0.72, 0.96)



# CRT-D:ICD Hazard Ratios for Prespecified Subgroups



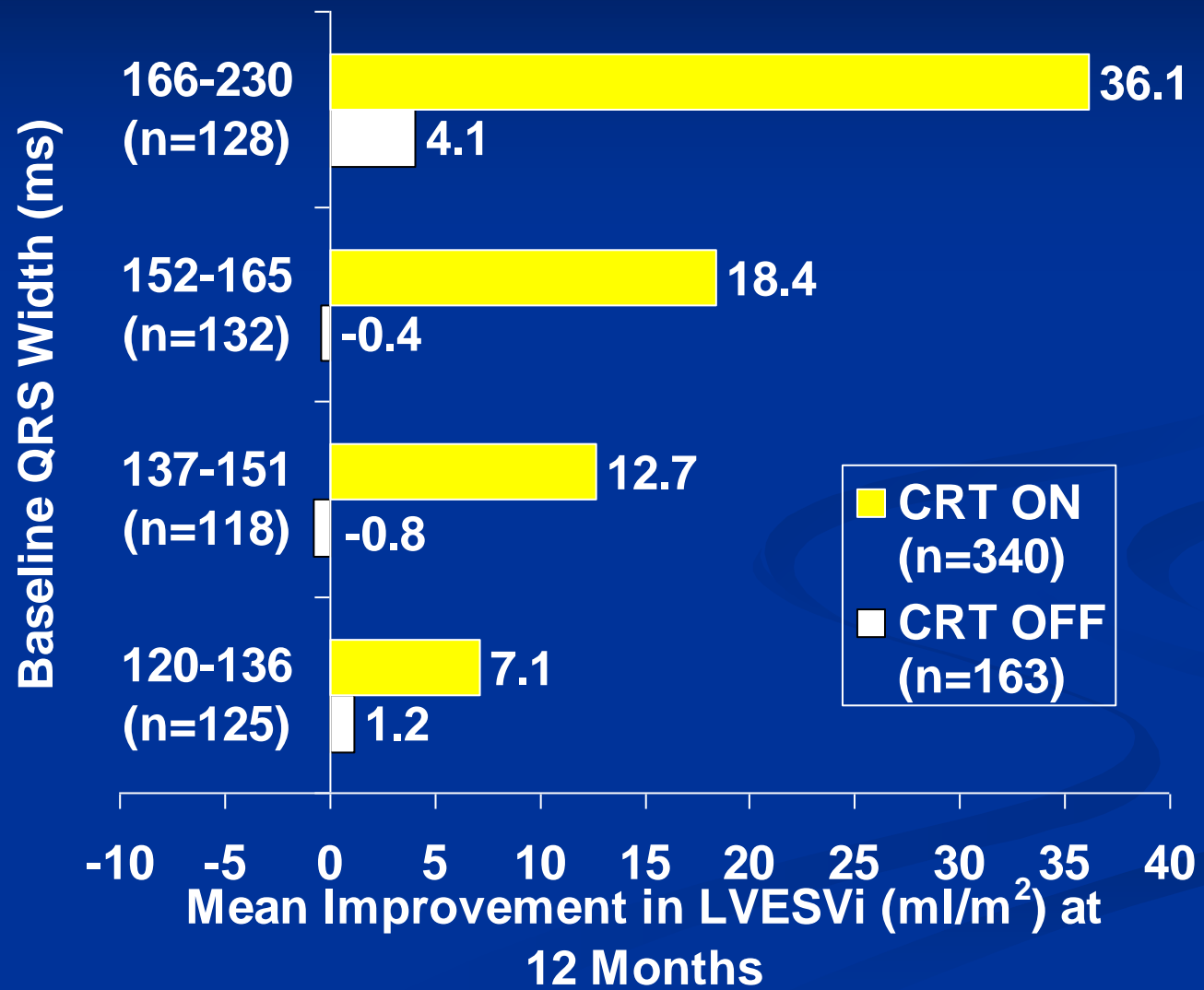
## Recommendation in patients with heart failure in NYHA function class II

Recommendation	Patient Population	Class	Level	Refs
CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression*	NYHA function class II LVEF≤35%, QRS≥150 ms, SR Optimal medical therapy	I	A	9, 20-22

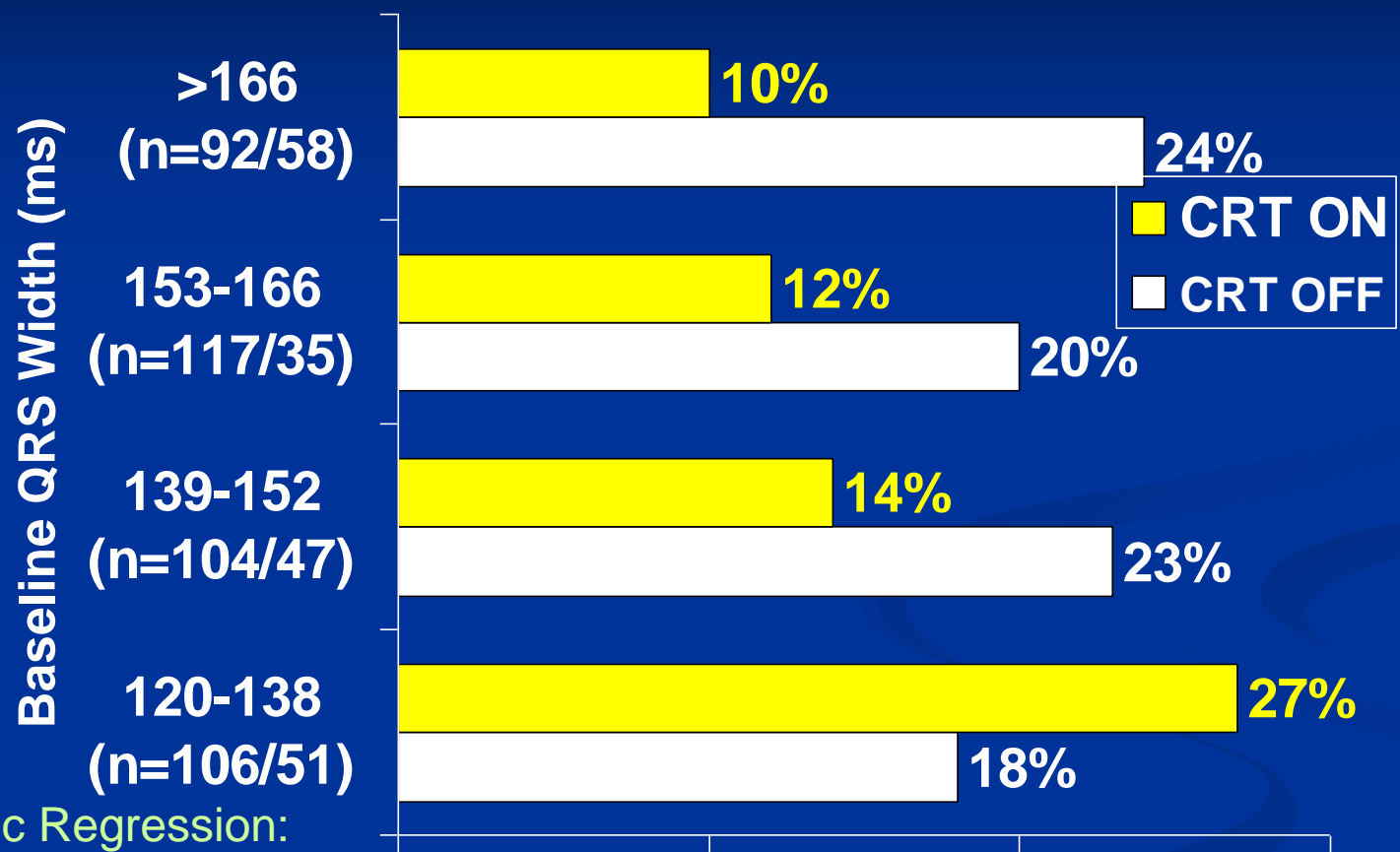
\* The guideline indication has been restricted to patients with HF in NYHA function class II with a QRS width ≥150 ms, a population with a high likelihood of a favourable response.

FDA restricted CRT in mild heart failure to LBBB

# Change in LVESVi by QRS Width



# Clinical Composite Score by QRS Width



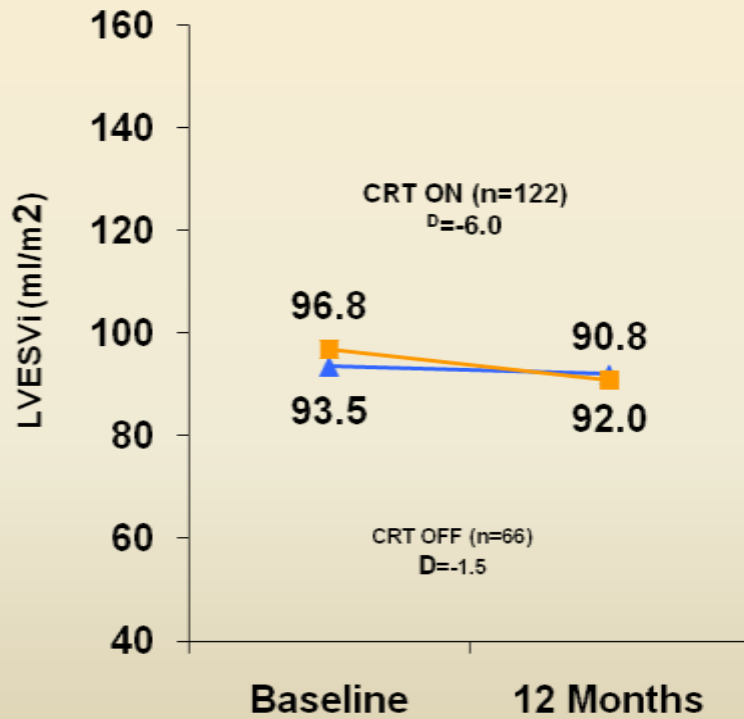
Logistic Regression:

Factor	P-value
Rand	0.01
QRS Width	0.08
Rand.*QRS	0.004

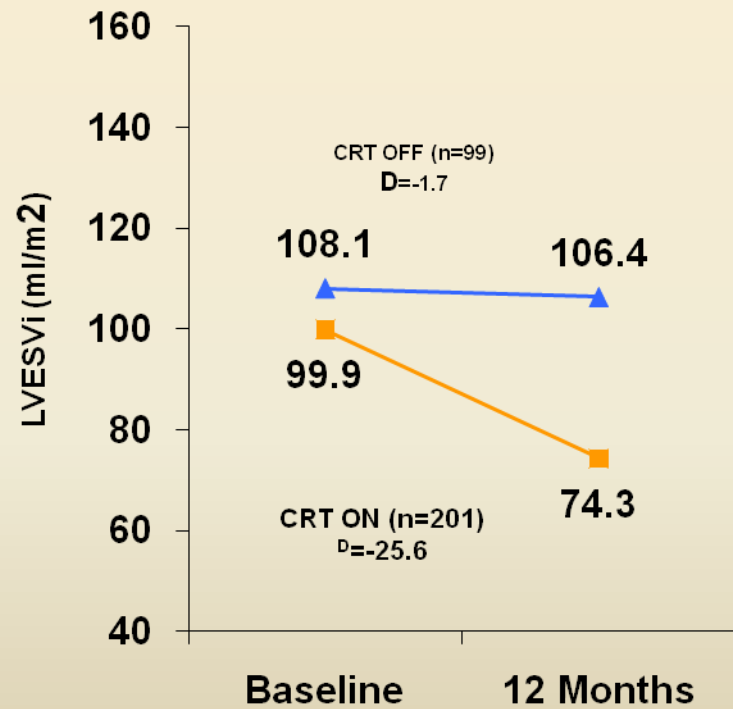
0% 10% 20% 30%  
% Worsened at 12 Months

# REVERSE : QRS Morphology

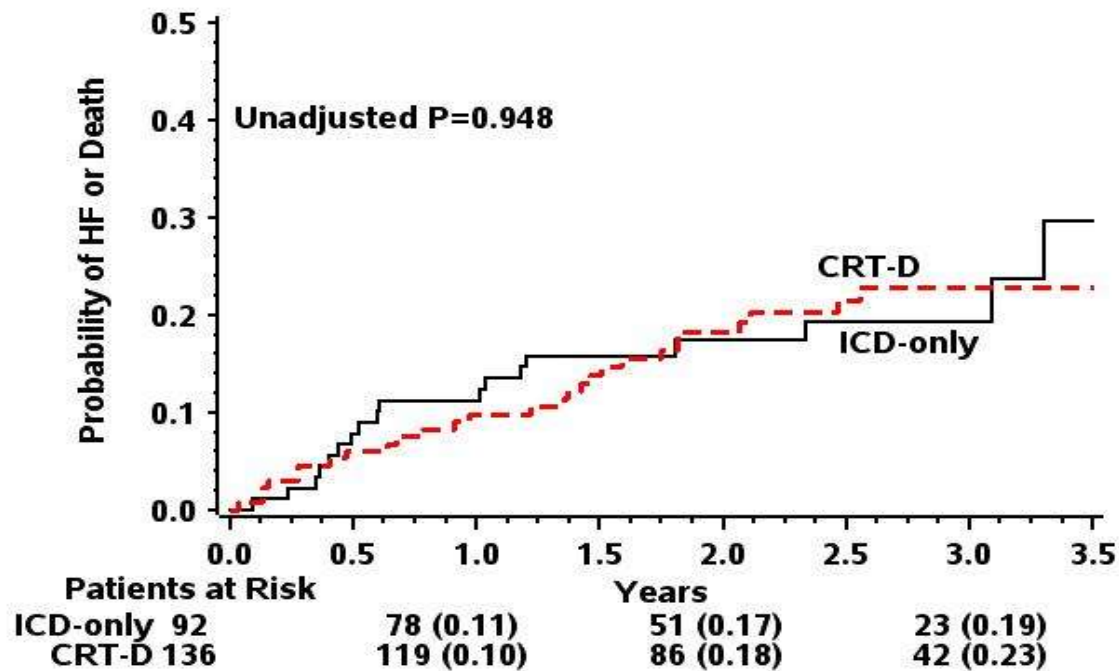
## RBBB



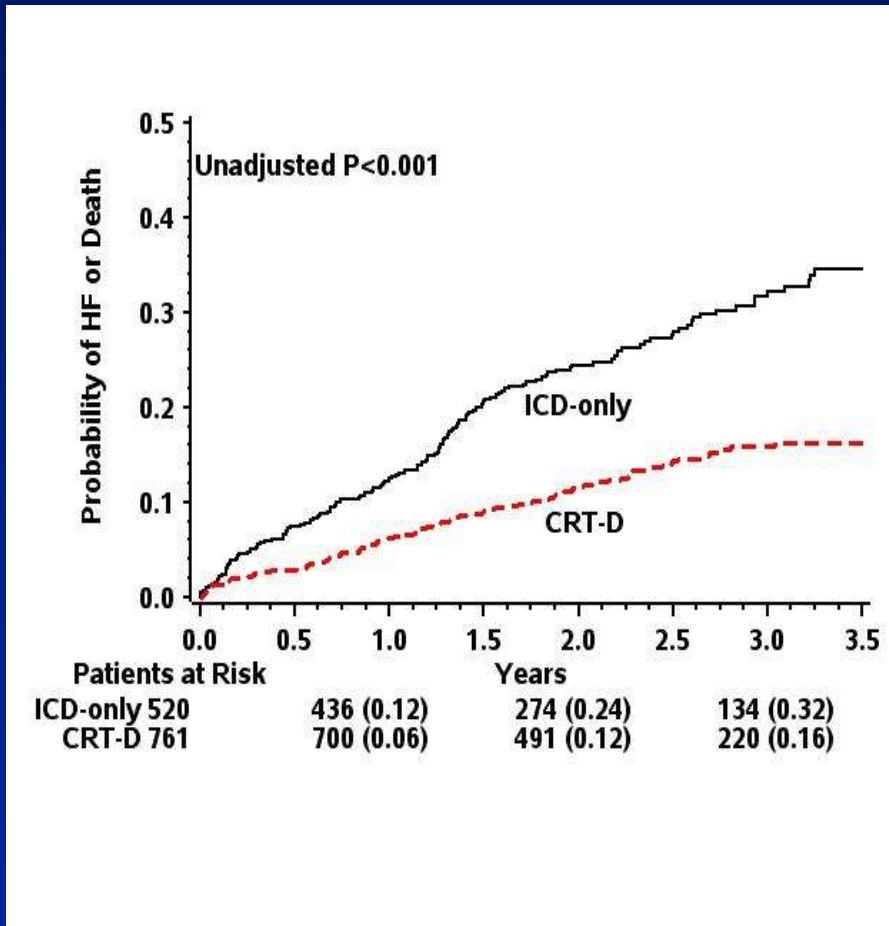
## LBBB



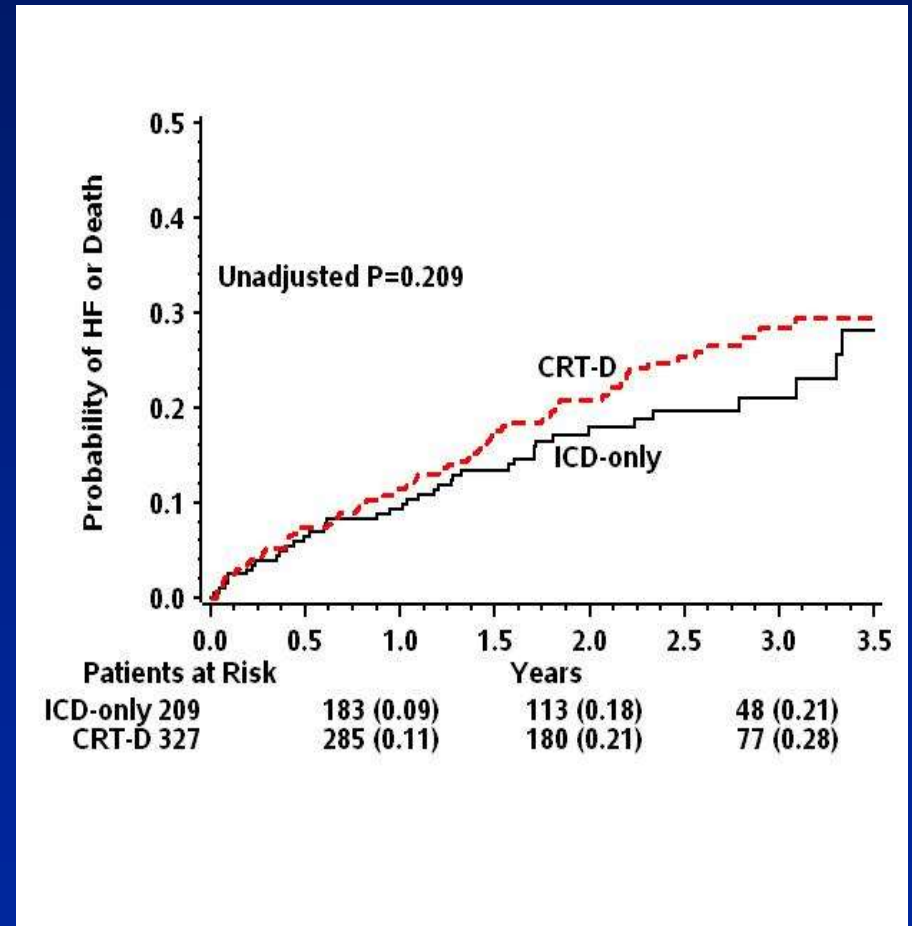
# RBBB in MADIT CRT



# Heart Failure (HF) Event or Death by QRS Pattern in MADIT-CRT Patients



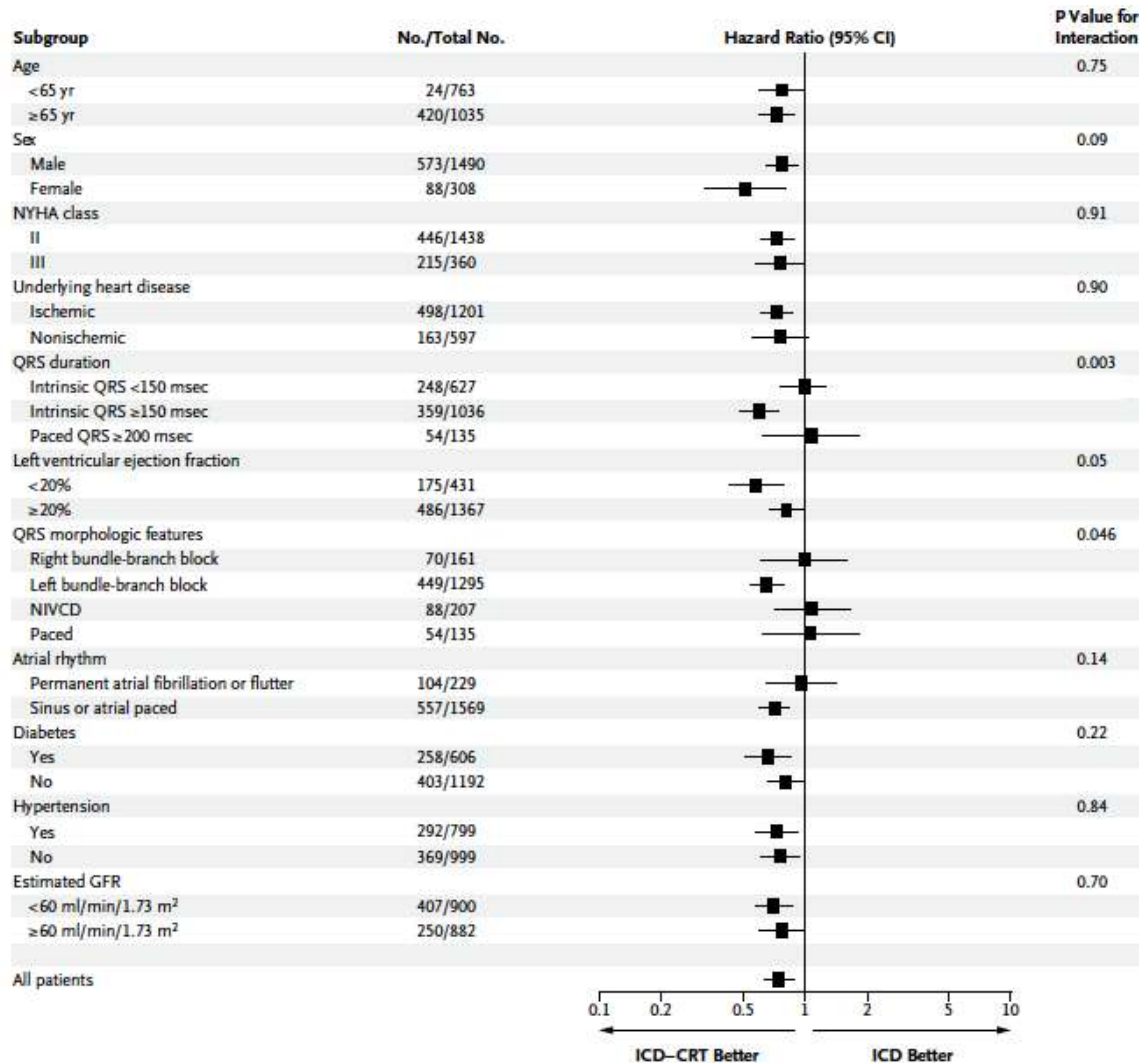
**LBBB**



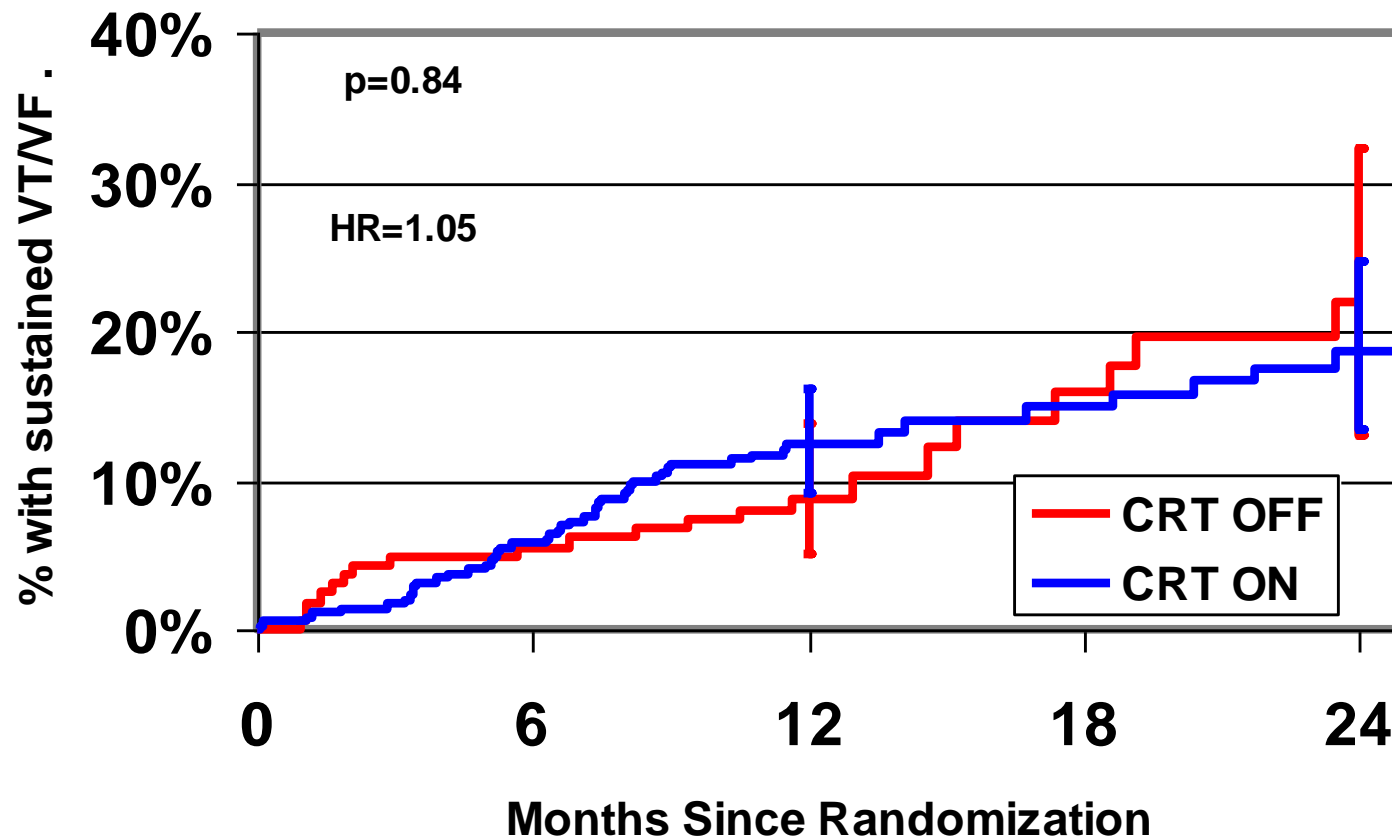
**Non-LBBB**



# Primary Outcome: Subgroup Analysis

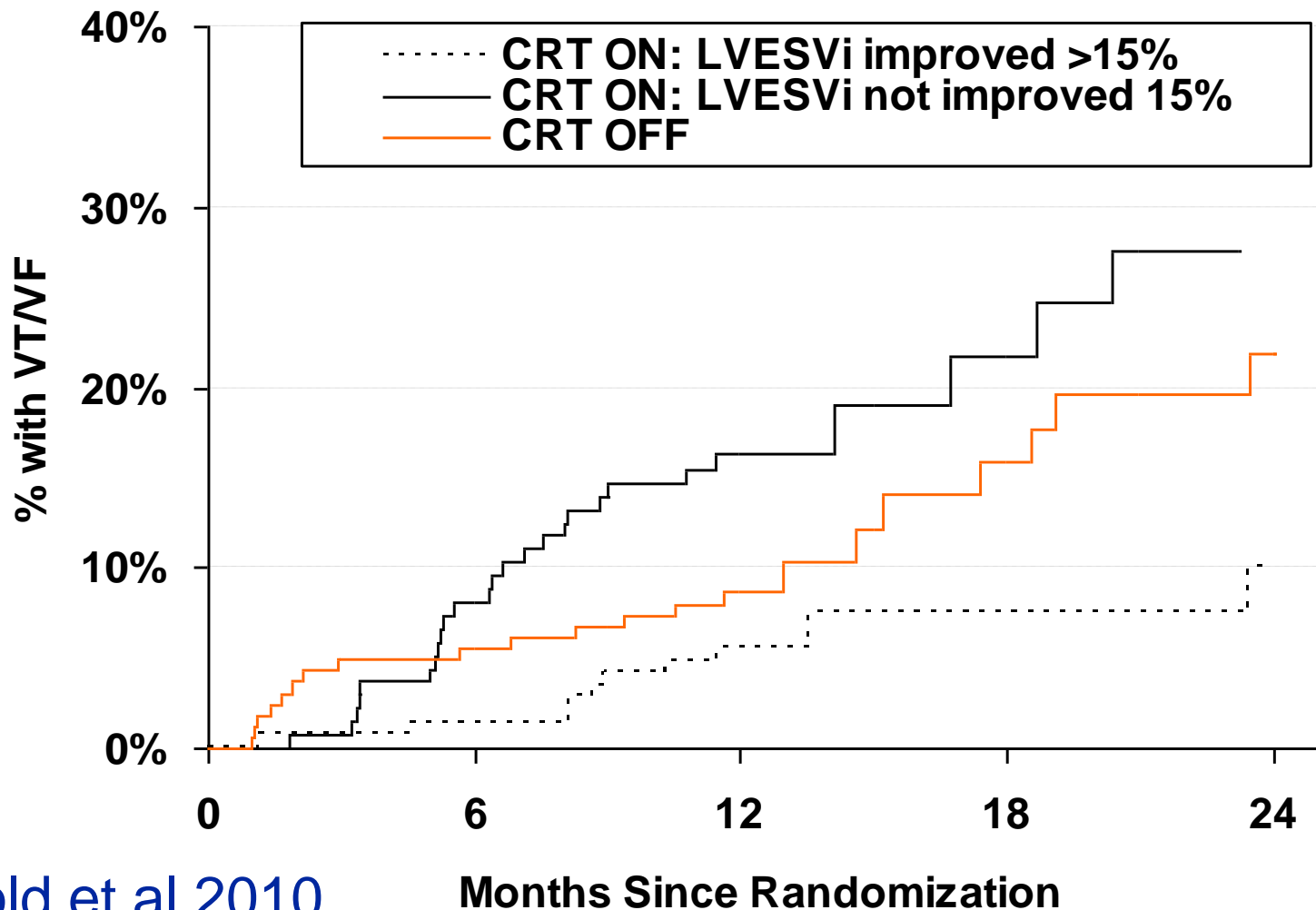


# Time to First VT/VF by Therapy



Number remaining	163	154	100	46	22
	345	323	196	96	41

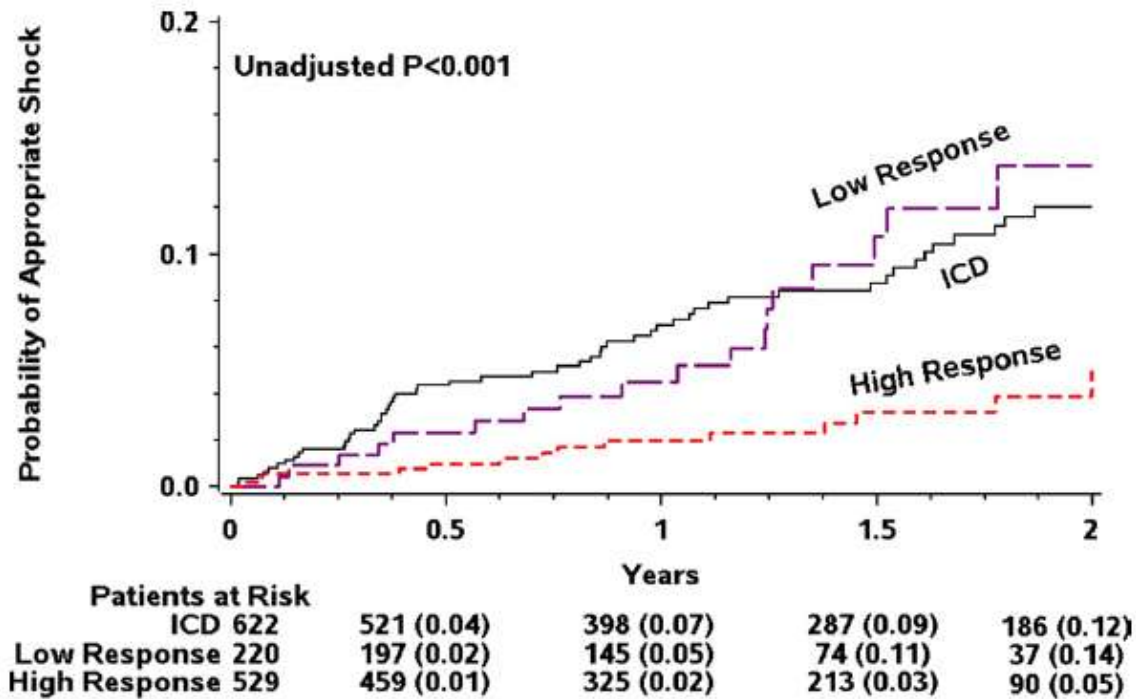
# Impact of Reverse Remodeling on VT



Gold et al 2010

Months Since Randomization

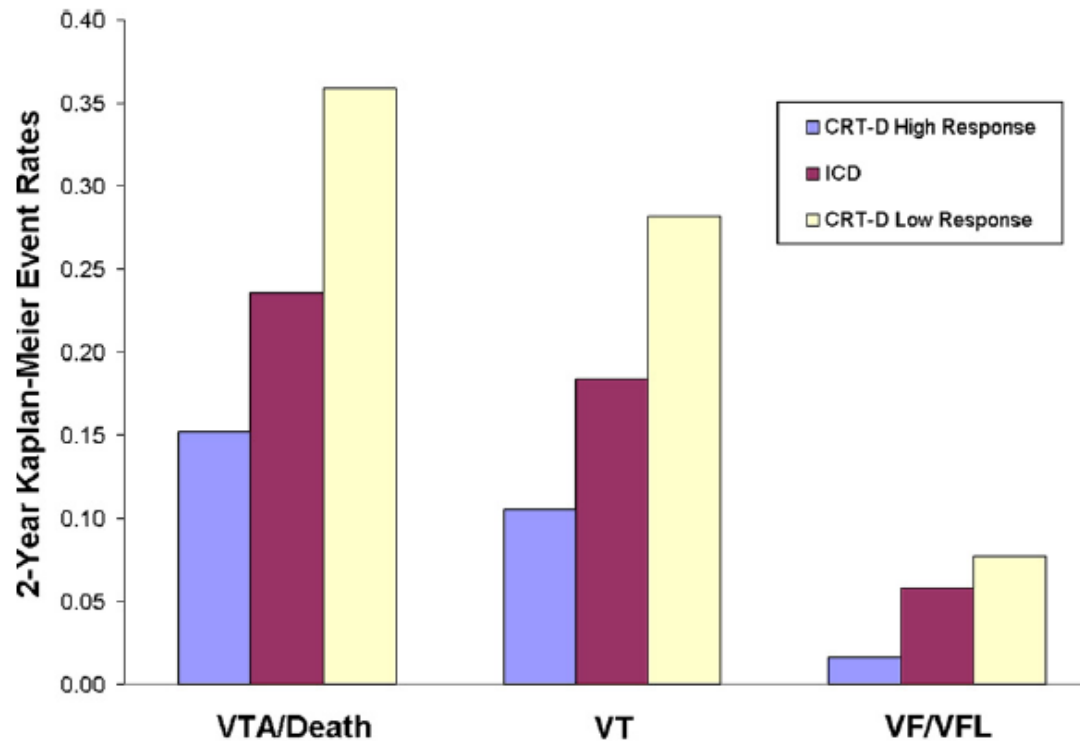
# MADIT CRT



**Figure 3** Probability of Appropriate Shock by Treatment and Echocardiographic Response

Kaplan-Meier cumulative probability of a first occurrence of appropriate ICD shock among ICD-only patients, low responders to CRT-D, and high responders to CRT-D. Abbreviations as in Figure 1.

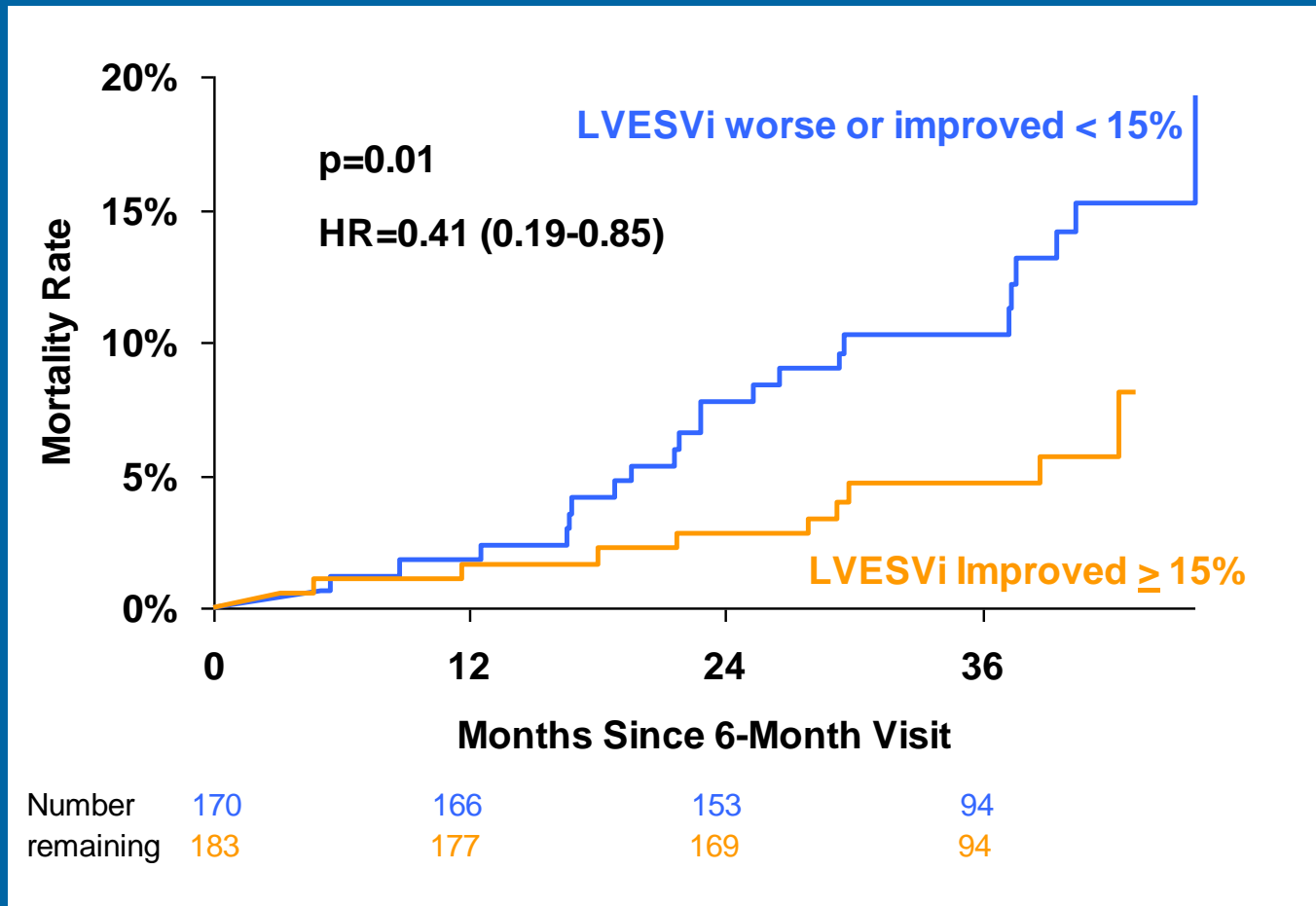
# MADIT CRT



**Figure 2** Two-Year Event Rate by Treatment and Echocardiographic Response

Two-year Kaplan-Meier ventricular tachyarrhythmia or death event rate among ICD-only patients, low responders to CRT-D, and high responders to CRT-D.  $p < 0.001$  for the overall difference among subgroups for all 3 endpoints shown. VF = ventricular fibrillation; VFL = ventricular flutter; VT = ventricular tachycardia; VTA = ventricular tachyarrhythmia; other abbreviations as in Figure 1.

# LVESVi Improvement vs. Mortality



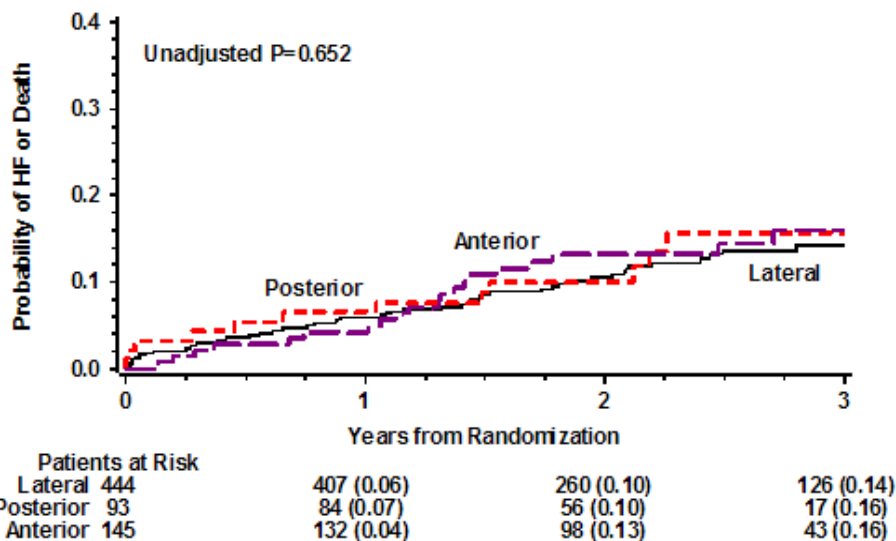
# Multi-variable Predictors of Mortality

<b>Variable</b>	<b>P-value</b>
Etiology of HF	0.0007
QRS duration	0.03
Baseline LVESVi	0.0001
Change in LVESVi	0.001

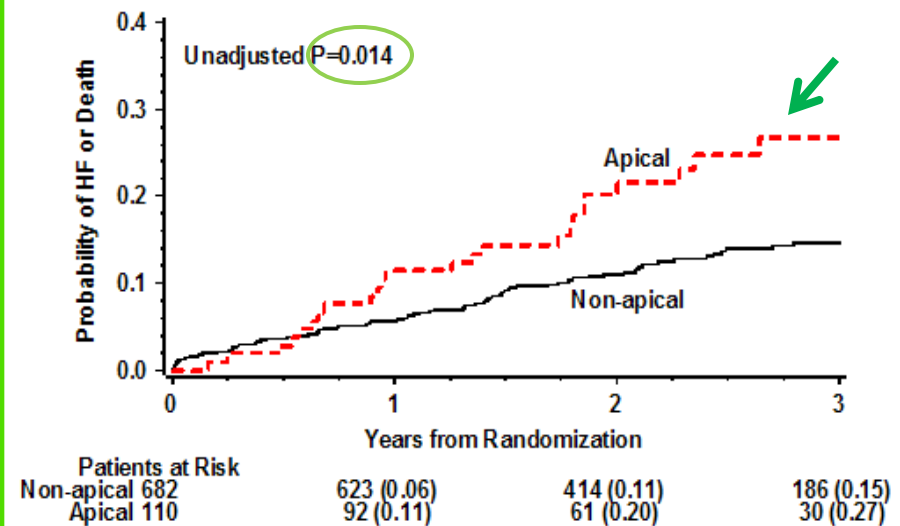
# LV Lead Position & Clinical Outcome

## Death &/or Heart Failure

Anterior, posterior and lateral position



Apical versus Non-apical position



- ◆ No difference amongst Anterior, Posterior and Lateral lead positions
- ◆ Apical lead positions associated with a significantly worse clinical outcome
- ◆ Differences maintained even after non-apical leads sub-stratified into mid-ventricular and basal

# Main aims of Health economics study

- Is CRT a cost-effective intervention in patients with mild to asymptomatic heart failure in comparison to CRT OFF-standard care?

Standard care → drug therapy + CRT OFF +/- ICD  
CRT → drug therapy + CRT ON +/- ICD

# Results (1)

Arm	Life Years Gained*	Costs†	QALYs†gained
CRT-OFF	7.46 (4.76 , 8.84)	€16,626 (€11.325 , €19.338)	5.18 (3.42 , 6.13)
CRT-ON	8.64 (6.78 , 9.33)	€28,081 (€20.559 , €30.598)	5.98 (4.81 , 6.49)
Incremental Values	<b>+ 1.18</b>	<b>+ €11.455</b>	<b>+ 0.80</b>

\* Undiscounted Values; † Discounted values; Mean (95% CI) reported for all key model outputs

**ICER or Cost-effectiveness ratio  $\Delta\text{Costs}/\Delta\text{QALYs}$ : €11.455 / 0.80 = €14.278 per QALY gained**

# Results (2)

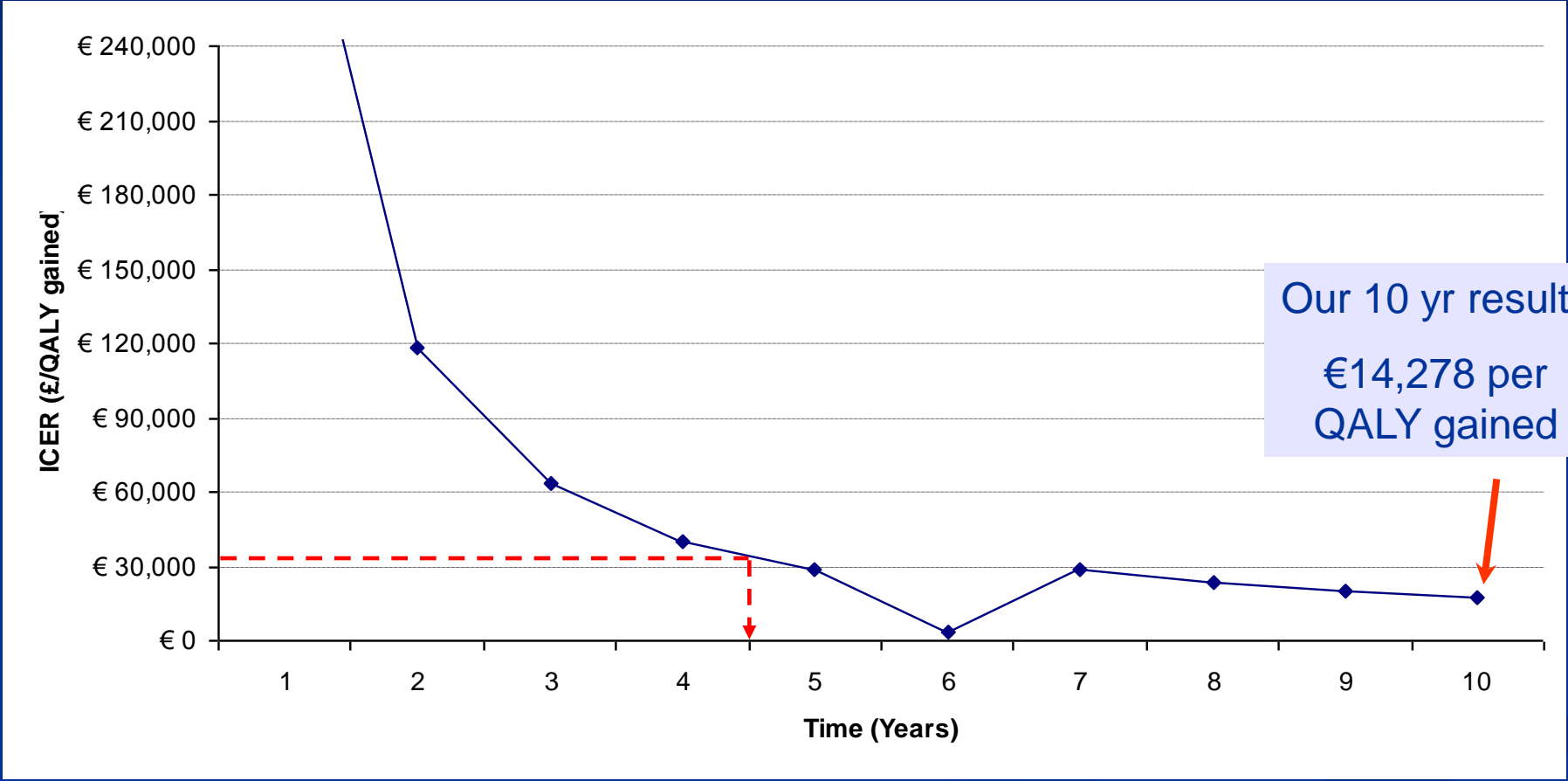
## Comparison with results from other CRT and ICD studies (NYHA II-IV)

Study/Source	ICER (Cost/QALY)	NNT (death avoided)	Time horizon for ICER
REVERSE	€14.278	4.9	10 years
CARE-HF	€ 7.538	5.6	Lifetime
COMPANION	\$19.600	6.3	7 years
NICE HTA CRT vs OPT	£16.738	Not calculable	Lifetime
SCD-HeFT	\$ 41.530	6.7	Lifetime

The cost/QALY in REVERSE is acceptable both overall and compared to other CRT and ICD studies

# Results (3) Key Sensitivity Analysis:

## Time for CRT to become cost-effective



Our 10 yr results  
€14,278 per  
QALY gained

CRT becomes cost-effective within 4.5 yrs

# What Else Have We Learned from CRT in Mild Heart Failure Trials?

- ◆ QRS duration is a strong predictor of response
- ◆ QRS morphology and gender are also strong predictors of response
- ◆ Reverse remodeling is important
- ◆ LV lead position is not so simple

# SUMMARY

- CRT is one of the most important therapeutic advance in HF in the last decade
- It is associated with improved functional status, reverse remodeling and reduced HF hospitalizations
- Comparable changes in LV structure and reductions in hospitalizations are noted in mild and severe heart failure patients. Similarly, the cost effectiveness is comparable to severe HF
- **Therefore, Patients with Left Ventricular Dysfunction and LBBB Should Receive CRT Regardless of Heart Failure Class**