CRT Indication :
NYHA Class III/IV vs. Class II

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최 기 준

CRT Indication in Korea

- NYHA functional class III or IV despite optimal medical Tx
- QRS duration ≥ 120msec
- LVEF ≤ 35%
- Sinus rhythm

ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities

Recommendations for Cardiac Resynchronization Therapy in Patients With Severe Systolic Heart Failure

JACC Vol. 51, No. 21, 2008

CLASS I

1. For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, CRT with or without an ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms with optimal recommended medical therapy. *(Level of Evidence: A)* (222,224,225,231)

CLASS IIa

1. For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy. *(Level of Evidence: B)* (220,231)
2. For patients with LVEF less than or equal to 35% with NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable. *(Level of Evidence: C)* (231)

2010 Focused Update of ESC Guidelines on device therapy in heart failure

An update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy

European Heart Journal (2010) **31**, 2677–2687

Recommendation in patients with heart failure in New York Heart Association function class III/IV

Recommendation	Patient population	Class[a]	Level[b]	Ref.[c]
CRT-P/CRT-D is recommended to reduce morbidity and mortality[d]	NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms, SR Optimal medical therapy Class IV patients should be ambulatory[e]	I	A	5–19

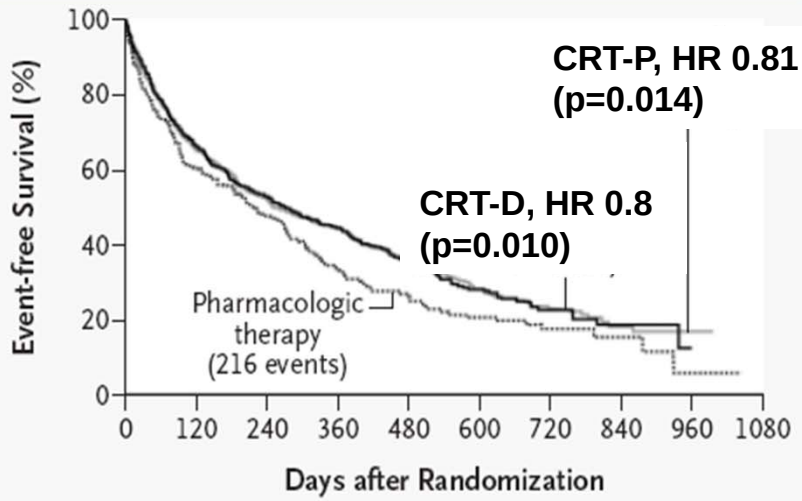
COMPANION study

N=1520, NYHA Class III/IV
EF<35%+ QRSd ≥120ms

Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure

N Engl J Med 2004;350:2140-50.

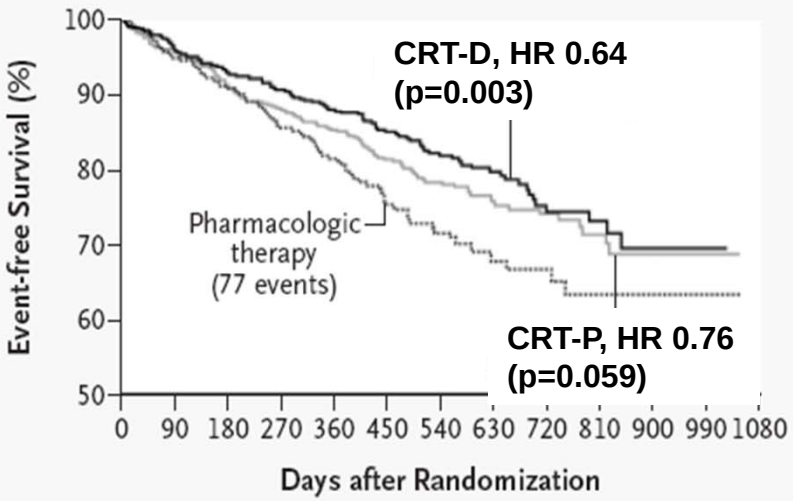
Primary End Point of Death from or Hospitalization for Any Cause



No. at Risk

Pharmacologic therapy	308	176	115	72	46	24	16	6	1
Pacemaker	617	384	294	228	146	73	36	14	3
Pacemaker–defibrillator	595	385	283	217	128	61	25	8	0

B Secondary End Point of Death from Any Cause



No. at Risk

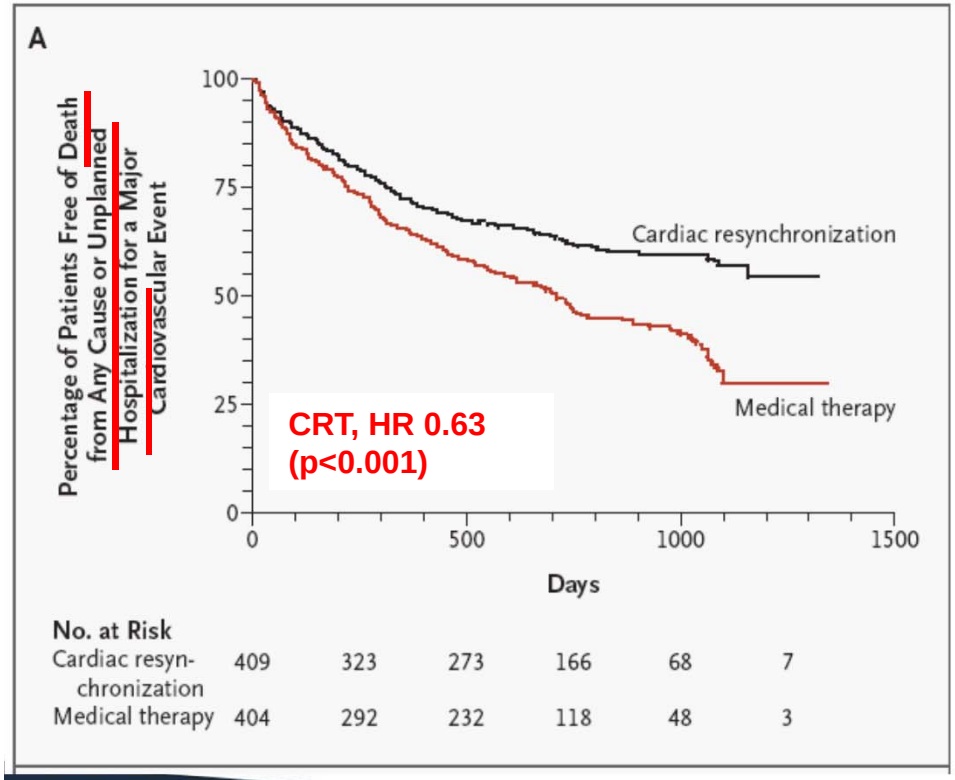
Pharmacologic therapy	308	284	255	217	186	141	94	57	45	25	4	2
Pacemaker	617	579	520	488	439	355	251	164	104	60	25	5
Pacemaker–defibrillator	595	555	517	470	420	331	219	148	95	47	21	1

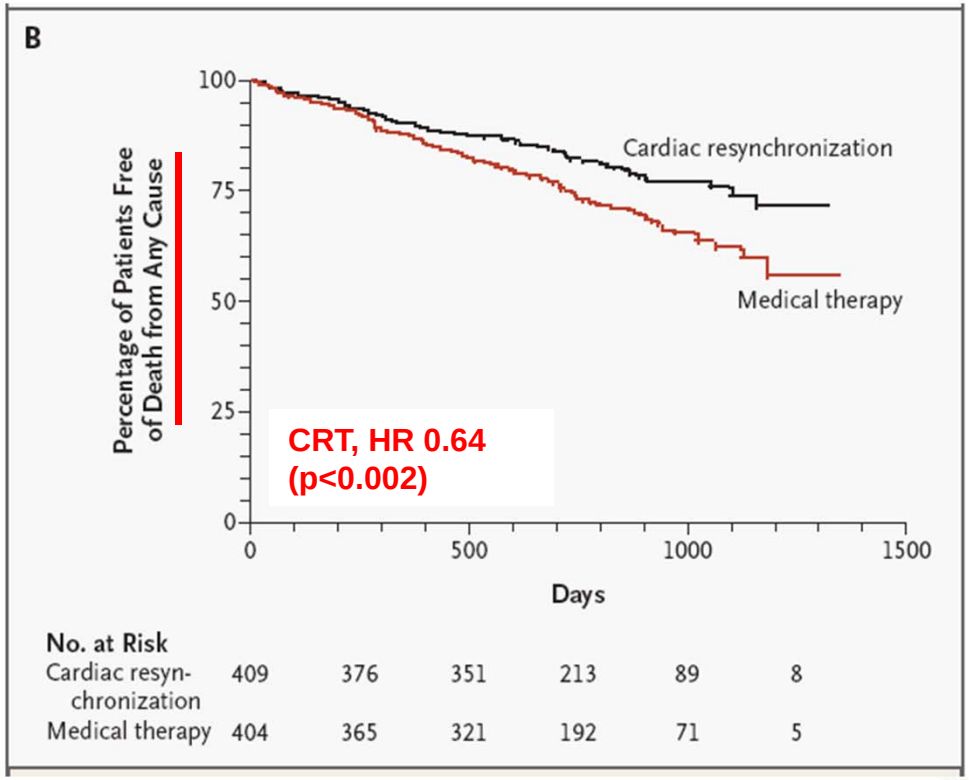
CARE-HF

N=813, NYHA Class III/IV, F/U 29.4m
EF<35%+ QRSd ≥120ms ± dyssynchrony

The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure

N Engl J Med 2005;352:1539-49.





Key points in CRT with NYHA III/IV

- LV dilatation no longer required in the Rx (new)
- Class IV patients should be ambulatory and reasonable expectation of survival with good functional status for >1y (new)
- Strongest evidence for typical LBBB pts.
- Similar level of evidence for CRT-P and CRT-D

European Heart Journal (2010) **31**, 2677–2687

CRT in NYHA I/II (mild to mod. HF)?

- **3 large randomized trials :**

1) **REVERSE study** *(JACC 2008;52:1834)*

- **REVERSE-Extension (European)**

(JACC 2009;54:1837)

2) **MADIT-CRT** *(NEJM 2009;361:1329)*

3) **RAFT** *(NEJM 2010;363:2385)*

1. REVERSE

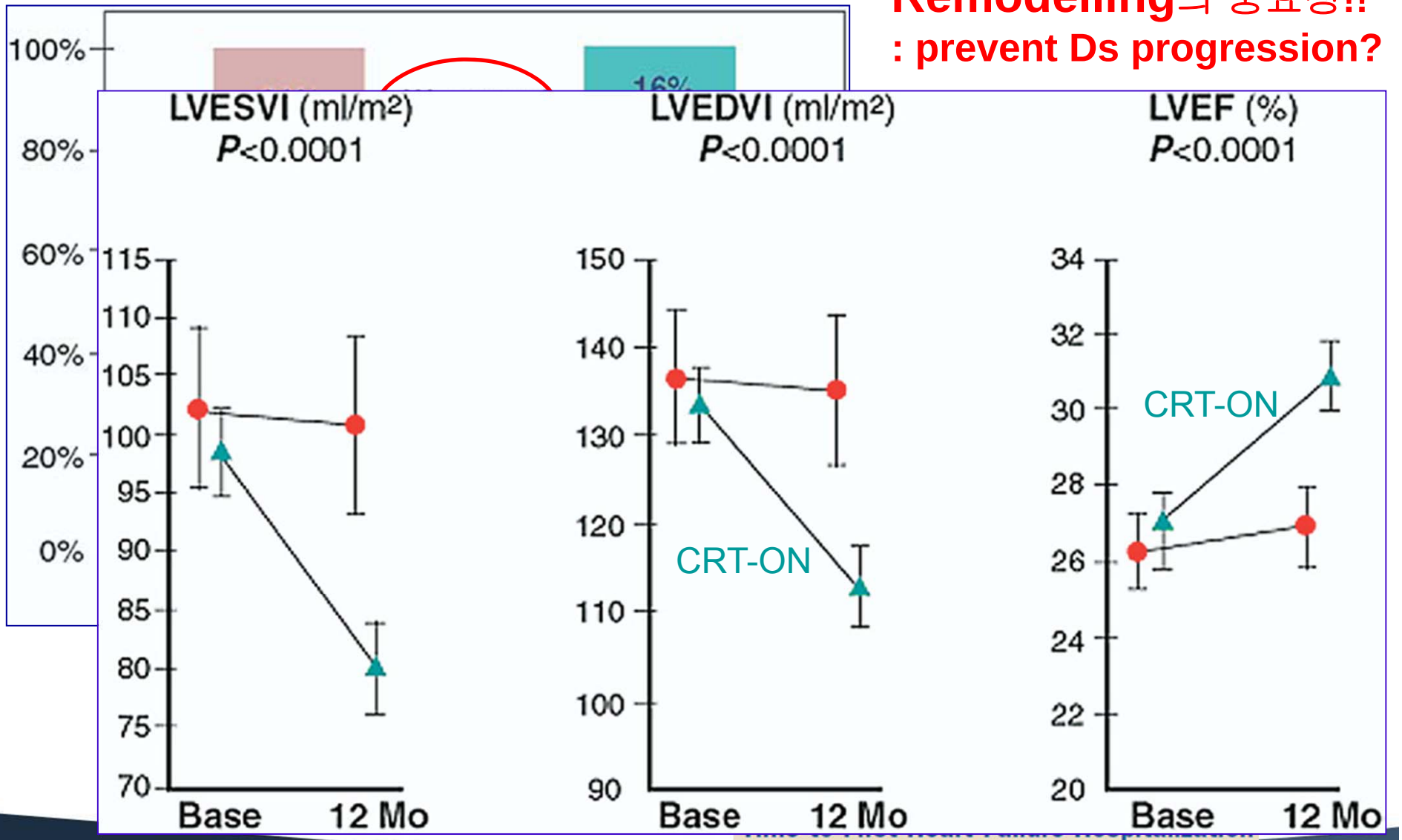
JACC 2008;52:1834

- N=610
- NYHA class I or II, SR, EF<40%, QRSd ≥ 120ms, LVDd ≥55mm
- ***Hx of HF symptom with class I***
- CRT-P(15%) or CRT-D
- Randomly assigned to CRT activated or off
- Primary end point : worsened HF

Secondary end point : Echo parameter

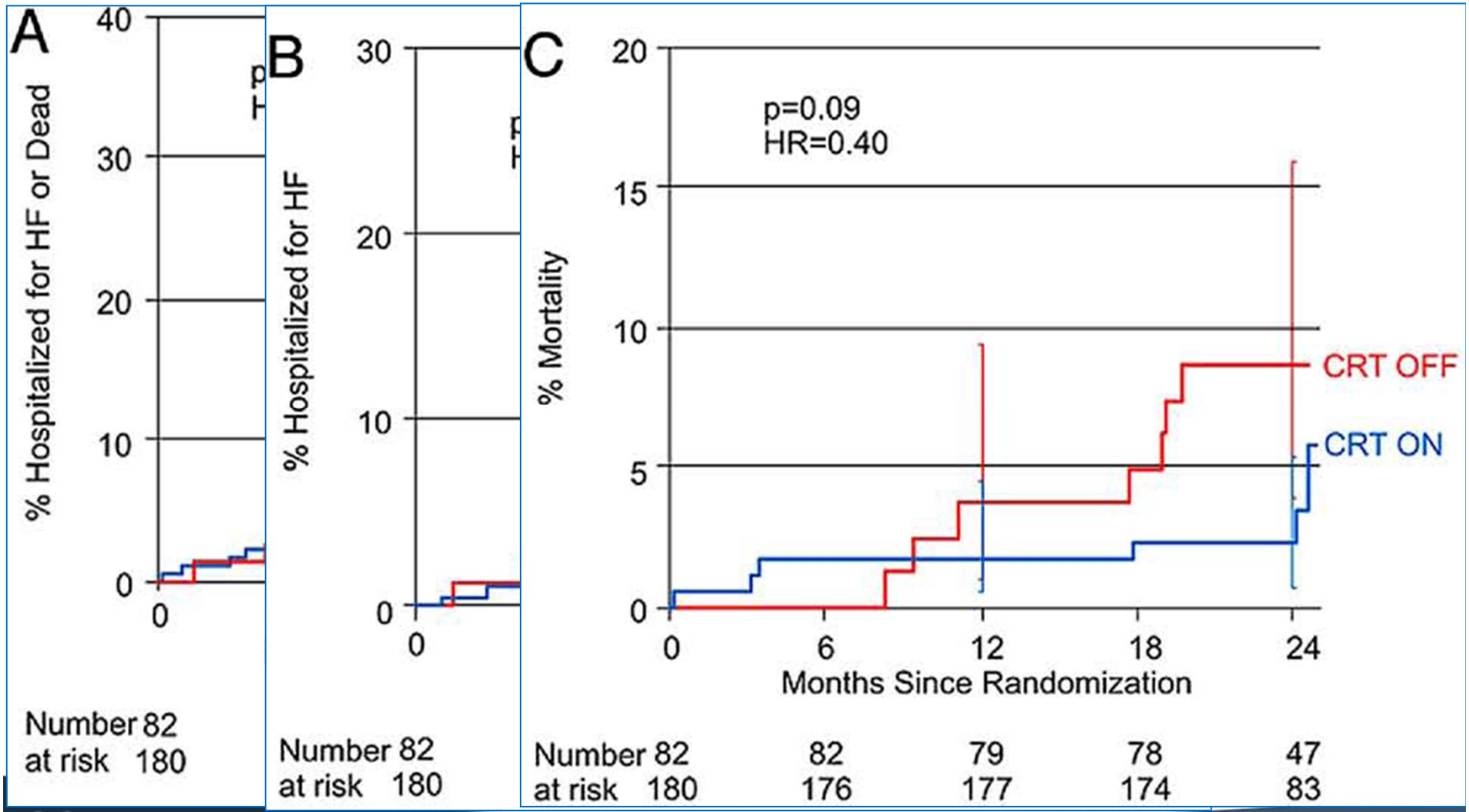
REVERSE

Remodelling의 중요성!!
: prevent Ds progression?



REVERSE - European cohort

J Am Coll Cardiol 2009;54:1837–46



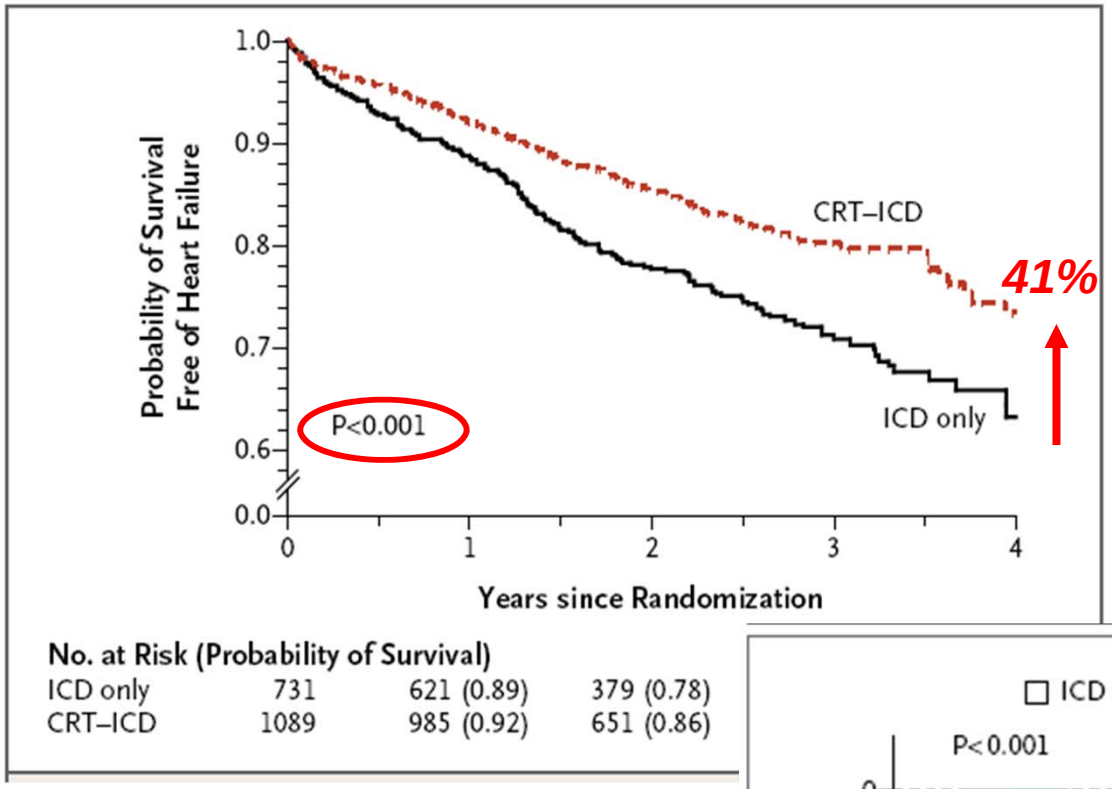
2. MADIT-CRT

NEJM 2009;361:1329

- N=1820, mean F/U : 2.4y
- NYHA class I(15%) of ischemic etiology or class II(84%) of any etiology
- SR, EF≤30%, QRSd ≥ 130ms
- ICD vs. CRT-D
- Primary end point : composite of any cause death and HF-related adverse events

MADIT-CRT

NEJM 2009;361:1329



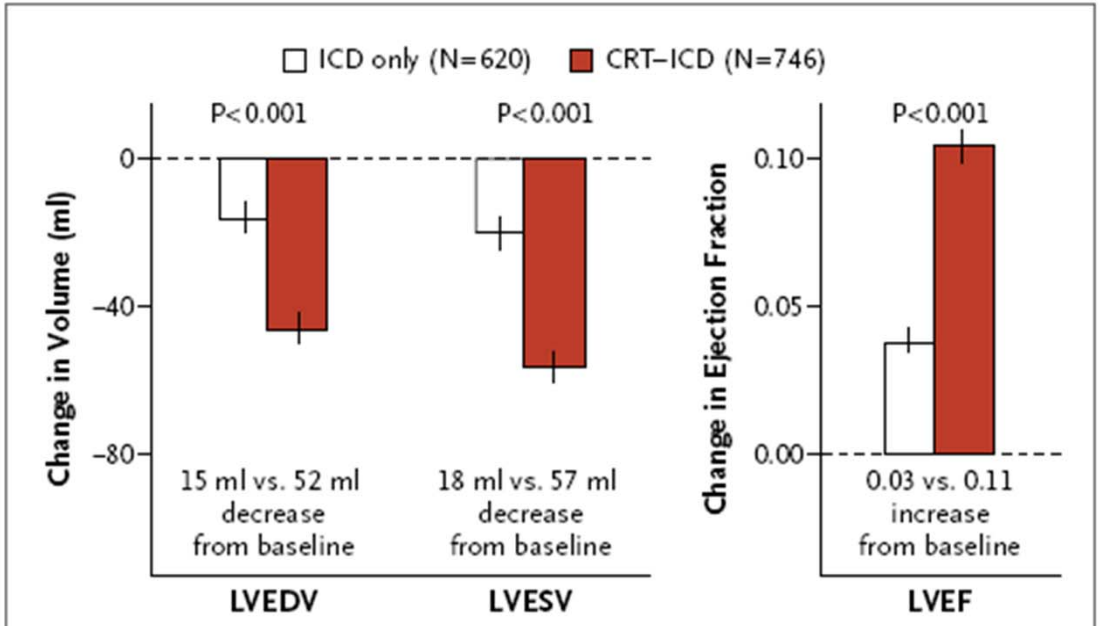


Figure 4. Changes in Mean Echocardiographic Left Ventricular Volumes and Ejection Fraction between Baseline and 1-Year Follow-up.

Table 2. Risk of Death or Heart Failure.*

Variable	ICD-Only Group	CRT–ICD Group	Hazard Ratio (95% CI)†	P Value
	no. (%)			
All patients	731	1089		
Death or heart failure‡	185 (25.3)	187 (17.2)	0.66 (0.52–0.84)§	0.001§
Heart failure only	167 (22.8)	151 (13.9)	0.59 (0.47–0.74)	<0.001
Death at any time¶	53 (7.3)	74 (6.8)	1.00 (0.69–1.44)	0.99
Patients with ischemic cardiomyopathy (NYHA class I or II)	401	598		
Death or heart failure‡	117 (29.2)	122 (20.4)	0.67 (0.52–0.88)	0.003
Heart failure only	105 (26.2)	96 (16.1)	0.58 (0.44–0.78)	<0.001
Death at any time¶	35 (8.7)	53 (8.9)	1.06 (0.68–1.64)	0.80
Patients with nonischemic cardiomyopathy (NYHA class II)	330	491		
Death or heart failure‡	68 (20.6)	65 (13.2)	0.62 (0.44–0.89)	0.01
Heart failure only	62 (18.8)	55 (11.2)	0.59 (0.41–0.87)	0.01
Death at any time¶	18 (5.5)	21 (4.3)	0.87 (0.44–1.70)	0.68

NEJM 2009;361:1329

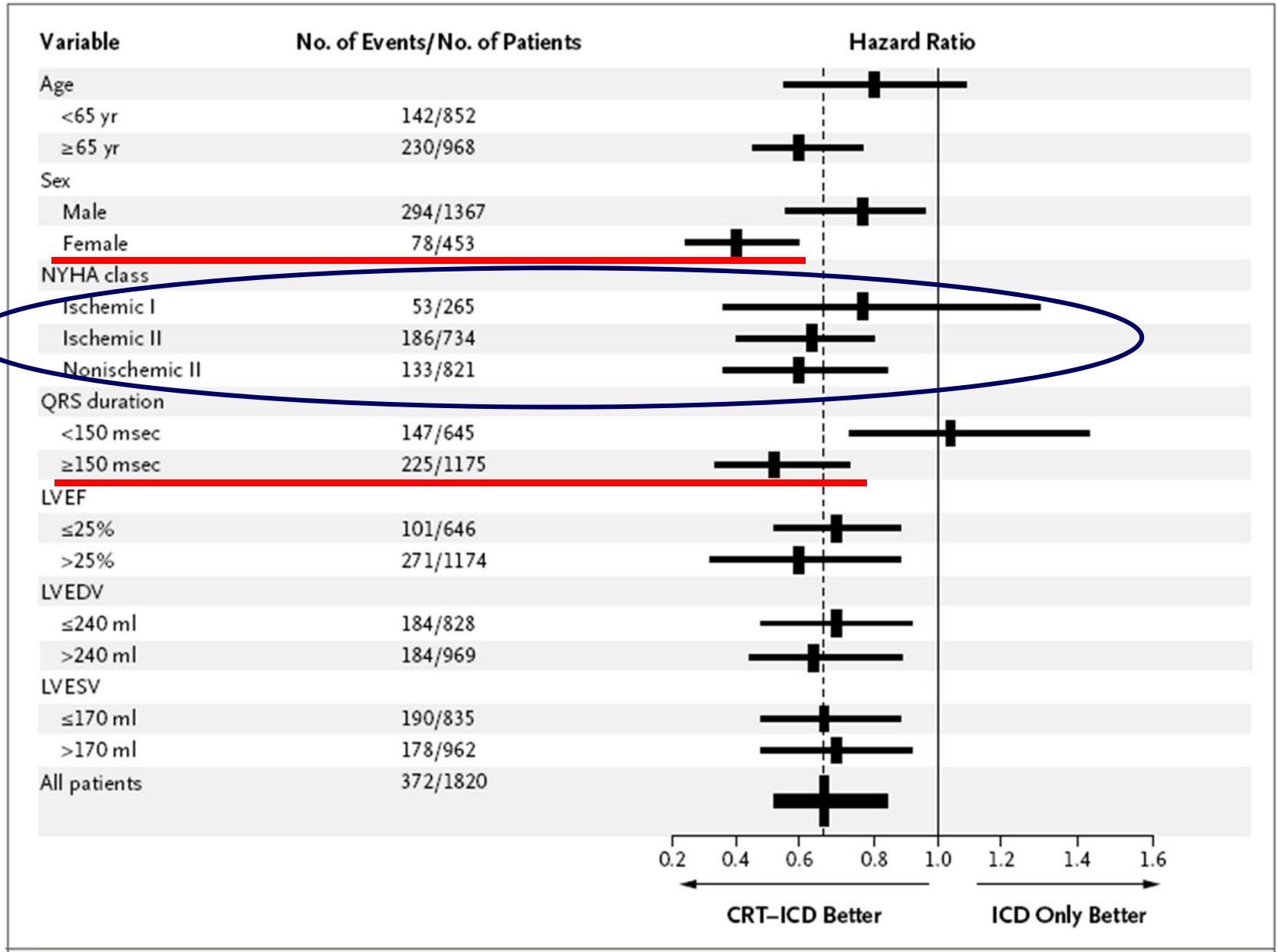


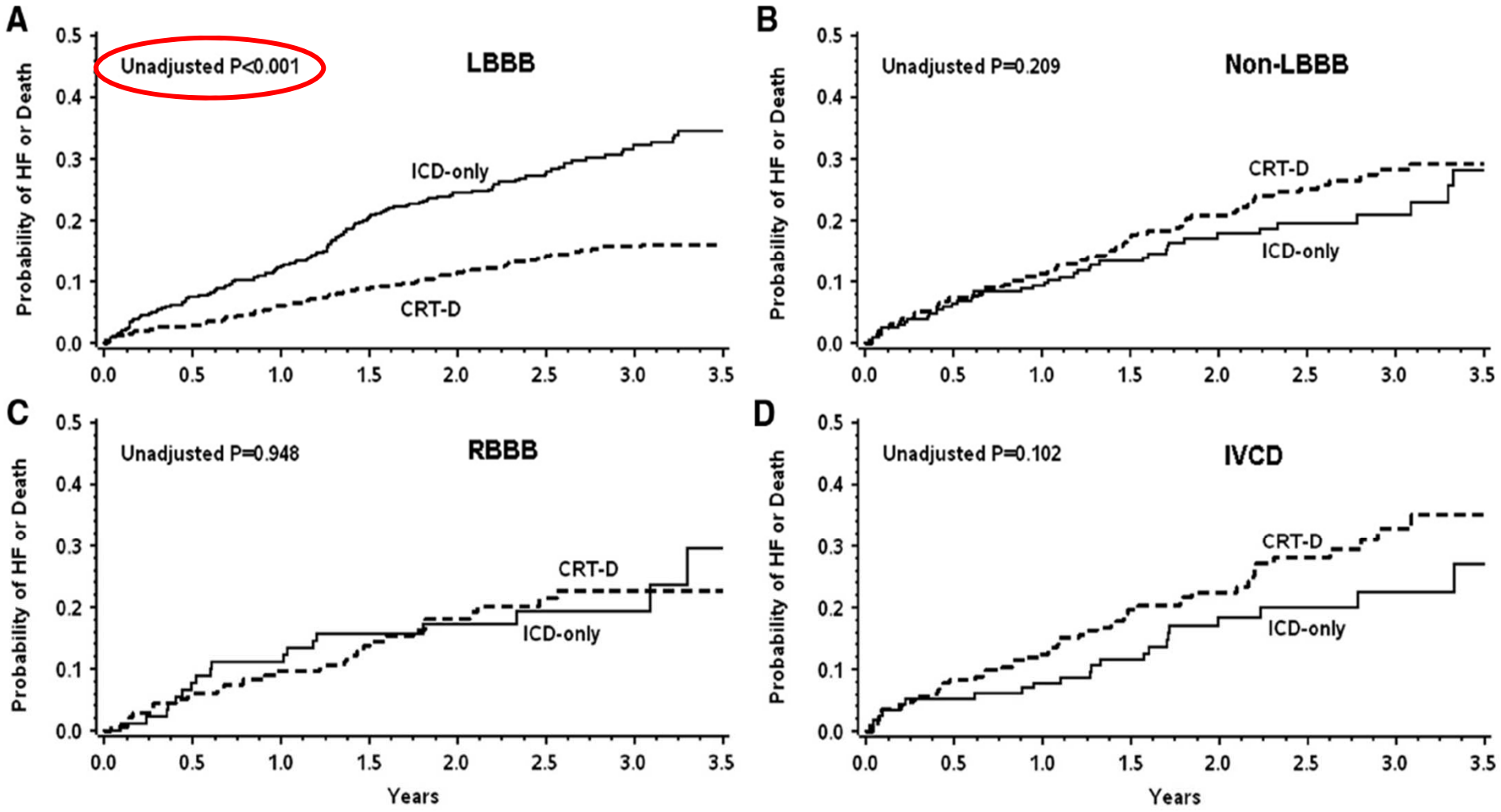
Figure 3. Risk of Death or Heart Failure, According to Selected Clinical Characteristics.

MADIT-CRT subgroup analysis

- **LBBB** vs. non-LBBB in MADIT-CRT *(Circulation. 2011;123:1061)*
  - In HF with NYHA class I/II, **significant clinical benefit from CRT-D in LBBB** (HR 0.47, P<0.001), vs non-LBBB(HR 1.24, P=0.25)
- More effective in **women** than in men with CRT in MADIT-CRT *(J Am Coll Cardiol. 2011;57:813)*
  - Significantly greater reduction in death or HF and all-cause mortality in women than men
  - Greater echo evidence of reverse remodeling in women than in men

Cumulative probability of HF event or death
(CRT-D versus ICD only)

Circulation. 2011;123:1061



heartwire | Comment | Print | Share | Cite | Tweet this | Text size

ARRHYTHMIA/EP

FDA approves new indications for CRT-D devices based on MADIT-CRT

SEPTEMBER 16, 2010 | Reed Miller

Natick, MA - The **FDA** is expanding the approved indications for three Boston Scientific cardiac resynchronization defibrillators (CRT-D) to include patients with milder heart failure and left bundle branch block (LBBB) [1].

The September 16 approval follows the advice of the agency's Circulatory System Devices Panel, which **voted in favor of the indication** expansion at its March 19 meeting, covered by **heartwire**. The latest approval expands the indication to also include patients with LBBB and NYHA class 2 or ischemic class 1 heart failure with an LVEF ≤30% and a QRS duration ≥130 ms. The new LVEF and electrocardiographic criteria are more restrictive than the current FDA-approved indication for CRT-D, which covers patients with NYHA class 3-4 heart failure, LVEF ≤35%, and a QRS ≥120 ms.

Boston Scientific's products are now the only CRT-D devices approved for the expanded indication. The company requested the new indication based on the results of the **Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy** (MADIT-CRT), which showed patients with CRT-D devices had a one-third lower risk of death or heart-failure events over 2.5 years than patients with regular ICDs. There was no significant difference in death, but a 41% difference in heart-failure events.

LBBB was a marker of increased benefit with CRT-D in a subgroup analysis, and its inclusion in the indication was one of the few areas of disagreement at the March advisory panel meeting. In patients with left bundle branch block—70% of the MADIT-CRT population—CRT-D reduced the risk of death and heart-failure events 57% compared with ICD alone.

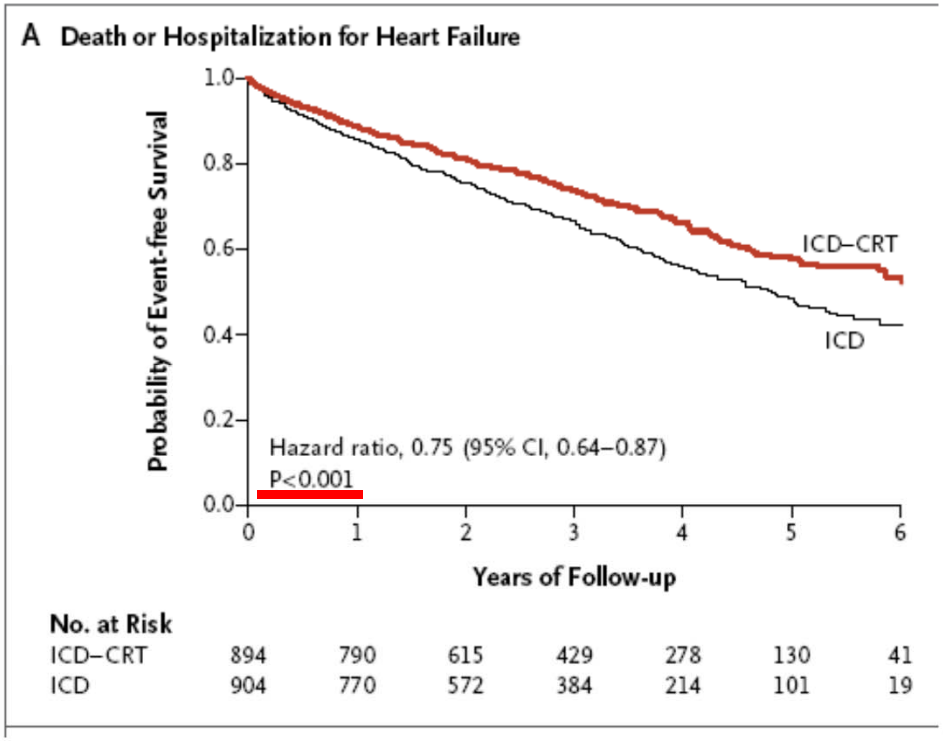
3. RAFT

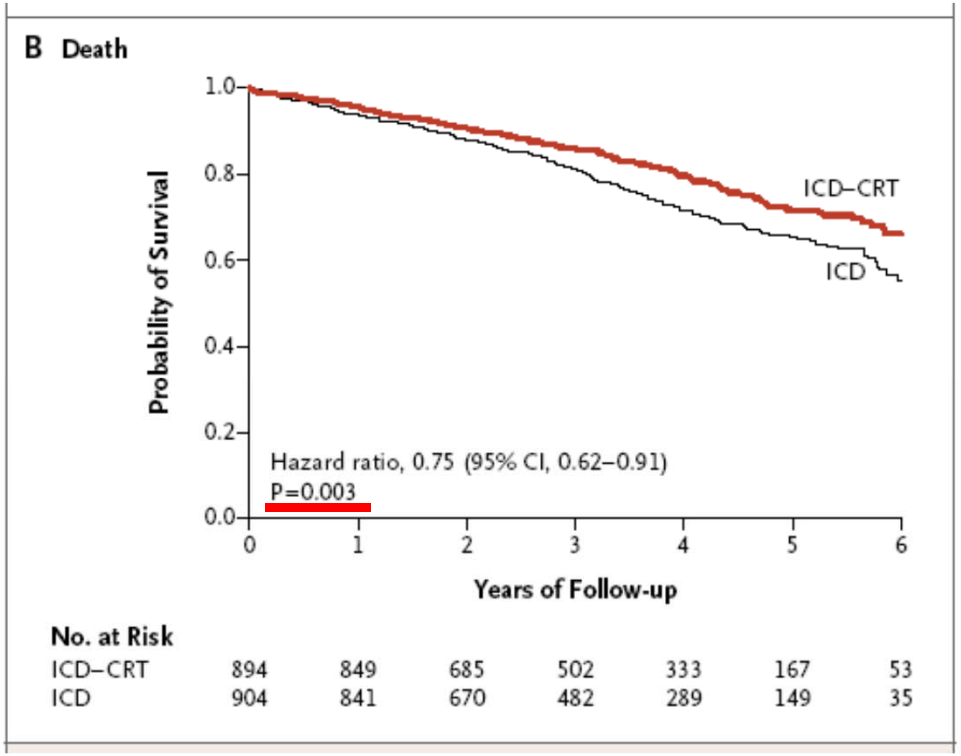
NEJM 2010;363:2385

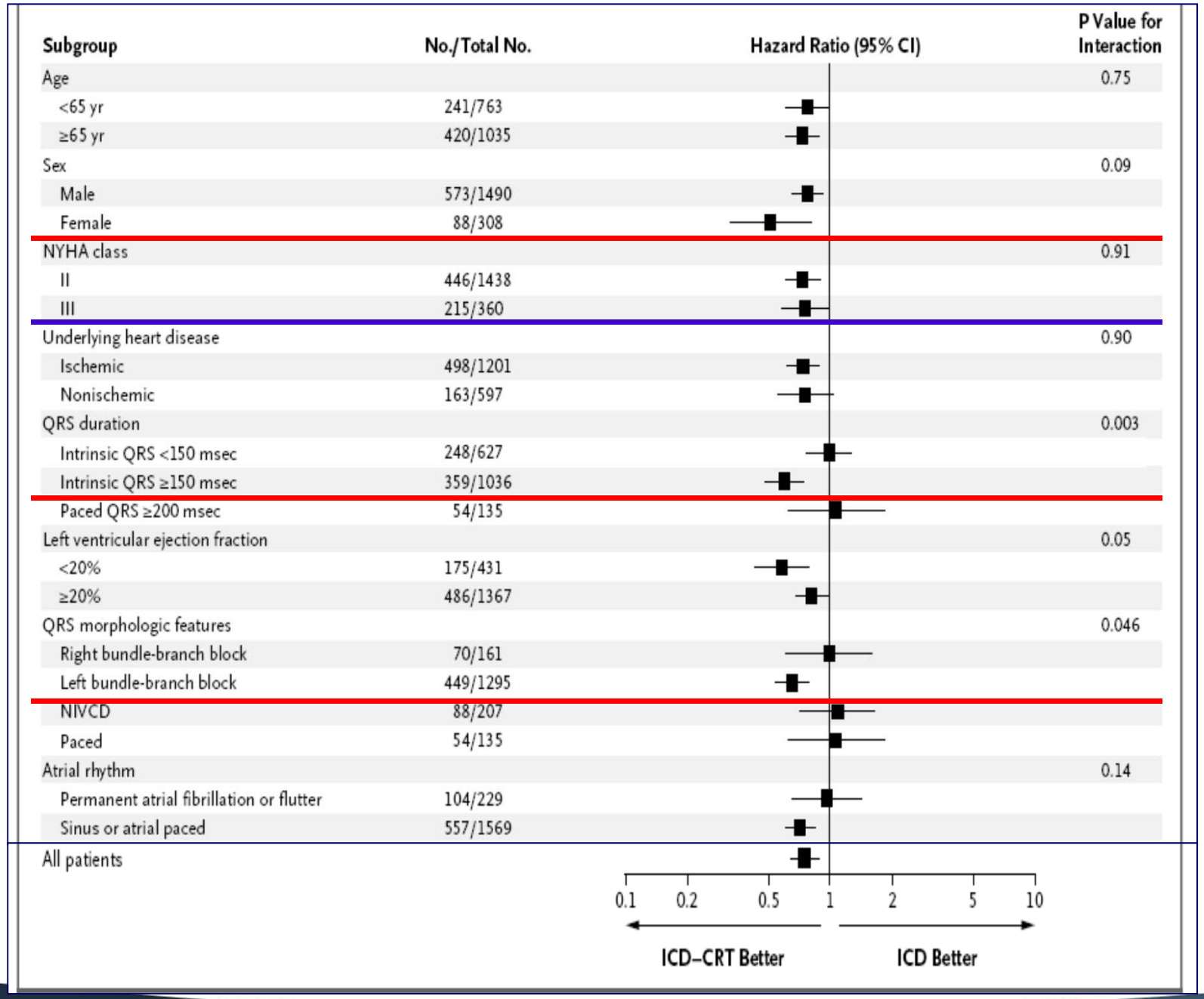
- N=1798
- NYHA class II or III, EF≤30%, QRSd ≥ 120ms or paced QRSd ≥ 200ms
- SR or Afib/AFL,
- ICD vs. CRT-D
- Primary end point : composite of any cause death or HF-hospitalization

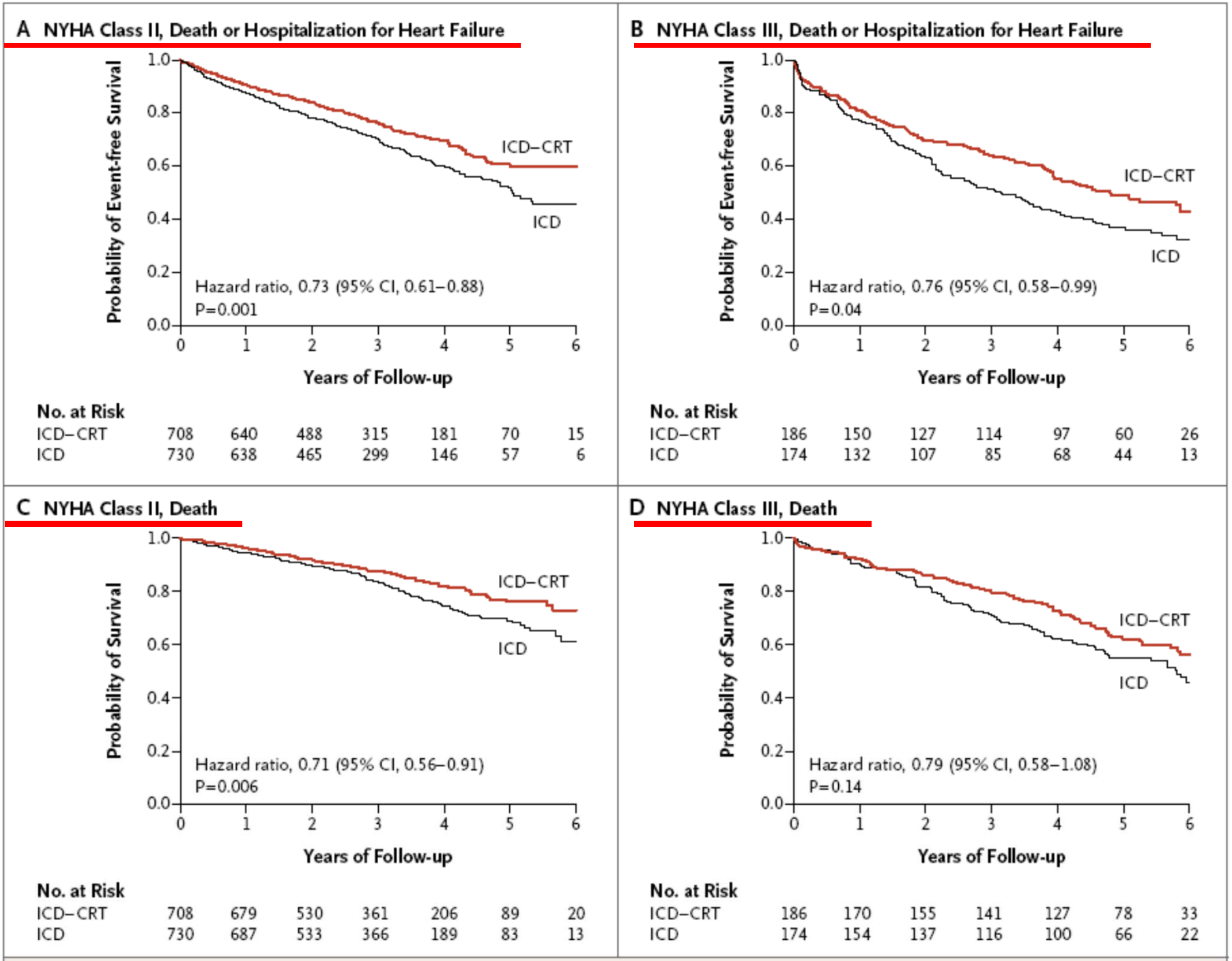
RAFT

NEJM 2010;363:2385






Subgroup
No./Total No.
Hazard Ratio (95% CI)
P Value for Interaction
Age 0.75
<65 yr 241/763
≥65 yr 420/1035
Sex 0.09
Male 573/1490
Female 88/308
NYHA class 0.91
II 446/1438
III 215/360
Underlying heart disease 0.90
Ischemic 498/1201
Nonischemic 163/597
QRS duration 0.003
Intrinsic QRS <150 msec 248/627
Intrinsic QRS ≥150 msec 359/1036
Paced QRS ≥200 msec 54/135
Left ventricular ejection fraction 0.05
<20% 175/431
≥20% 486/1367
QRS morphologic features 0.046
Right bundle-branch block 70/161
Left bundle-branch block 449/1295
NIVCD 88/207
Paced 54/135
Atrial rhythm 0.14
Permanent atrial fibrillation or flutter 104/229
Sinus or atrial paced 557/1569
All patients
0.1
0.2
0.5
1
2
5
10
ICD–CRT Better
ICD Better


A NYHA Class II, Death or Hospitalization for Heart Failure
Probability of Event-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
ICD–CRT
ICD
Hazard ratio, 0.73 (95% CI, 0.61–0.88)
P=0.001
0 1 2 3 4 5 6
Years of Follow-up
No. at Risk
ICD–CRT 708 640 488 315 181 70 15
ICD 730 638 465 299 146 57 6
B NYHA Class III, Death or Hospitalization for Heart Failure
Probability of Event-free Survival
ICD–CRT
ICD
Hazard ratio, 0.76 (95% CI, 0.58–0.99)
P=0.04
Years of Follow-up
No. at Risk
ICD–CRT 186 150 127 114 97 60 26
ICD 174 132 107 85 68 44 13
C NYHA Class II, Death
Probability of Survival
ICD–CRT
ICD
Hazard ratio, 0.71 (95% CI, 0.56–0.91)
P=0.006
Years of Follow-up
No. at Risk
ICD–CRT 708 679 530 361 206 89 20
ICD 730 687 533 366 189 83 13
D NYHA Class III, Death
Probability of Survival
ICD–CRT
ICD
Hazard ratio, 0.79 (95% CI, 0.58–1.08)
P=0.14
Years of Follow-up
No. at Risk
ICD–CRT 186 170 155 141 127 78 33
ICD 174 154 137 116 100 66 22

Comparison of trials

Table 1. Comparison of clinical trials evaluating clinical effects of cardiac resynchronization therapy in mild to moderate heart failure.

Trial	REVERSE	REVERSE European	MADIT-CRT	RAFT
Number of patients	610	262	1,820	1,798
Design of trial				
Inclusion criteria:				
NYHA class	I/II	I/II	I/II	II/III
EF	≤ 40%	≤ 40%	≤ 30%	≤ 30%
QRS	≥ 120 ms	≥ 120 ms	≥ 130 ms	≥ 120 ms/ /≥ 200 ms paced
Primary endpoint	HF clinical composite score	HF clinical composite score	HF event or death	HF hospitalizations or death
Intervention	CRT-D or CRT *vs* no CRT (2:1)	CRT-D or CRT *vs* no CRT (2:1)	CRT-D *vs* ICD (3:2)	CRT-D *vs* ICD (1:1)

(Cardiol J 2010; 17, 6: 543–548)

Trial	REVERSE	REVERSE European	MADIT-CRT	RAFT
Results of trial				
Follow-up	12 months	24 months	28 months	40 months
NYHA class:				
I	18%	17%	15%	–
II	82%	83%	85%	80%
III	–	–	–	20%
Mean EF	27%	28%	24%	23%
Mean QRS	153 ms	153 ms	158 ms	158 ms
Left bundle branch block	NR	NR	70%	72%
HF or death:				
Comparison arm	NR	24%*	25.3%	40.3%
CRT/CRT-D arm	NR	12%*	17.2%	33.2%
Hazard ratio (p value)	NR	0.38 (0.003)	0.66 (0.001)	0.75 (< 0.001)
HF hospitalization:				
Comparison arm	7%	18.4%	22.8%	26.1%
CRT/CRT-D arm	3%	7.8%	13.9%	19.5%
Hazard ratio (p value)	0.47 (0.03)	0.39 (0.01)	0.59 (< 0.001)	0.68 (< 0.001)
Death:				
Comparison arm	2.2%	8.6%	7.3%	26.1%
CRT/CRT-D arm	1.6%	5.7%	6.8%	20.8%
Hazard ratio (p value)	NR (0.63)	0.40 (0.09)	1.00 (0.99)	0.75 (0.003)

MADIT-CRT vs. RAFT

- Both trials showed significant reduction in primary endpoint (HF event or death) : 34% reduction in MADIT-CRT, 25% reduction in RAFT
- **Only RAFT showed significant reduction in mortality** (not in MADIT-CRT)
  - RAFT, more advanced HF patients (20% class III)
  - 20% 2y year mortality in RAFT vs 6% in MADIT-CRT (25% in COMPANION, 18% in CARE-HF : NYHA class III/IV)

Cardiol J 2010;17:543

Key points in CRT with NYHA I/II

- Recent trials in mild HF demonstrated reduced morbidity
- NYHA class I : 18% of REVERSE(previous HF Sx+) and 15% MADIT-CRT – clinical outcome?
- Improvement primarily in patients with QRSd ≥150ms and/or typical LBBB
- Favorable response in women with LBBB, in MADIT-CRT
- Survival advantage?
- In MADIT-CRT, reverse remodelling predictive of clinical improvement

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Recommendation in patients with heart failure in New York Heart Association function class II

Recommendation	Patient population	Class[a]	Level[b]	Ref.[c]
CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression[d]	NYHA function class II LVEF ≤35%, QRS ≥150 ms, SR Optimal medical therapy	I	A	9, 20–22

Recommendation in patients with heart failure in New York Heart Association function class III/IV

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