Long-term benefit of CRT

How can we improve it?

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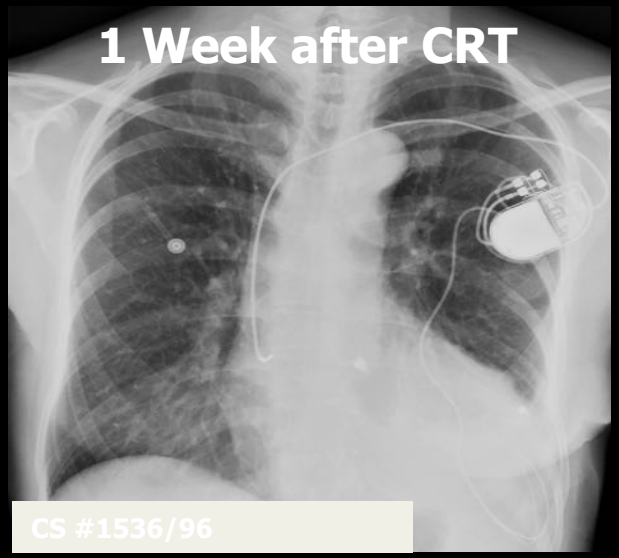
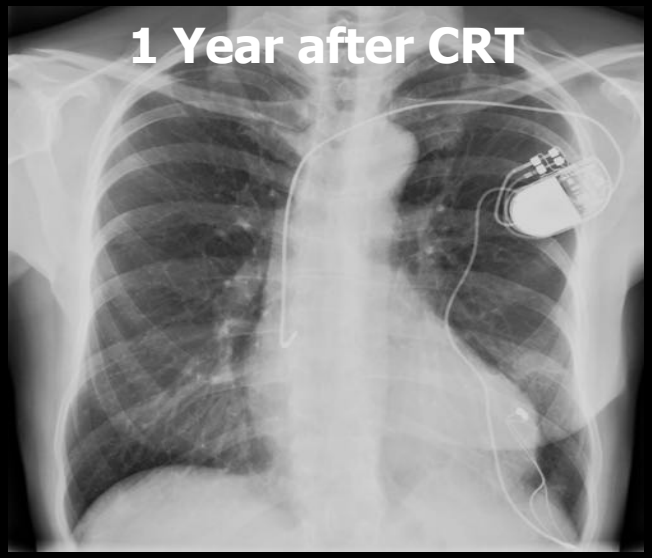
MY CONFLICTS OF INTEREST ARE

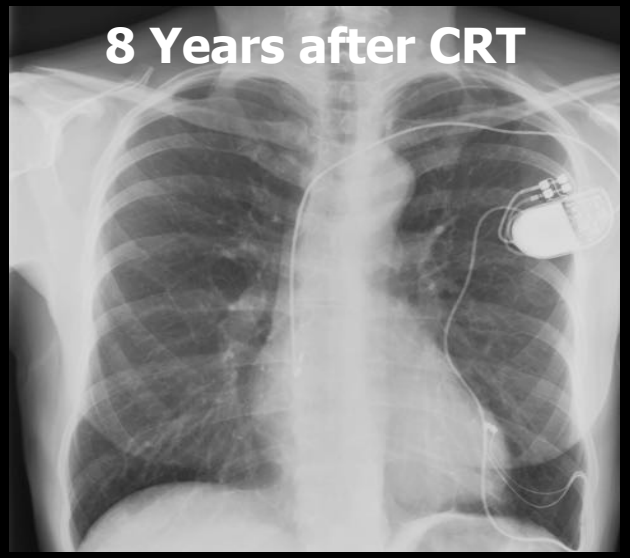
Lecture honoraria (LH,)
Research grants (RG)
Consulting (C)

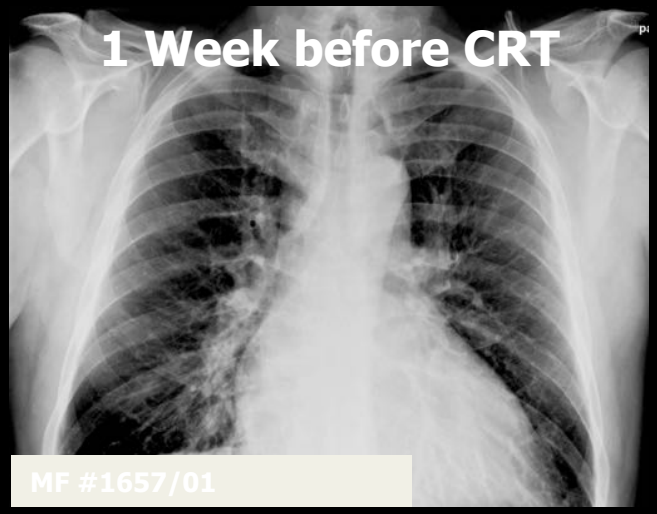
Boston Scientific, Inc. (RG,LH)
ZOLL-Lifecor Corp. (RG,C,LH)

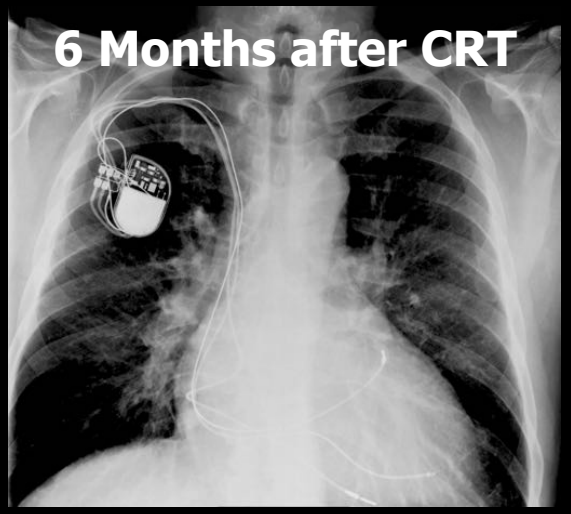
Long-term reverse remodeling with CRT

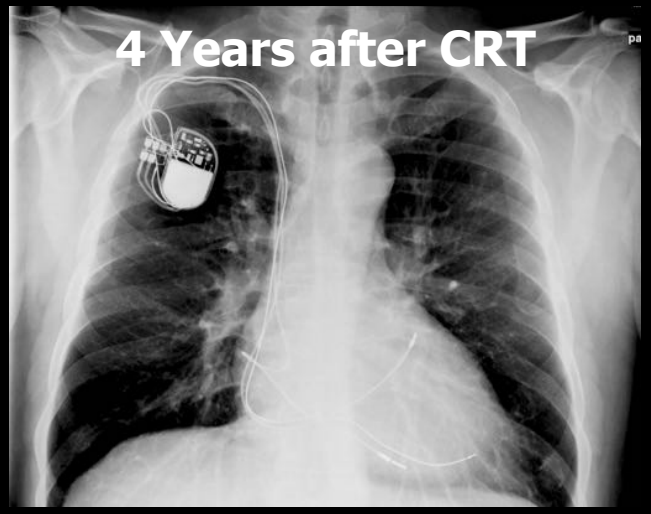






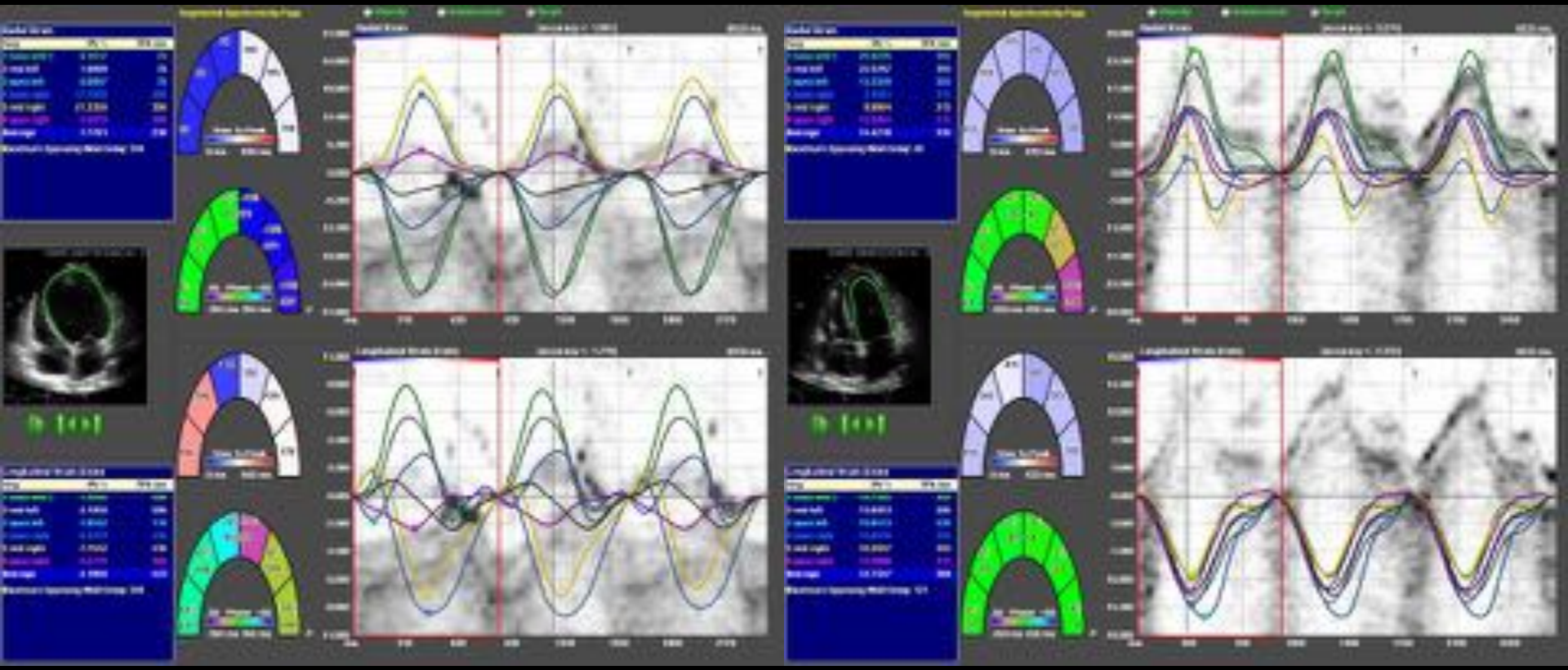






2 Patients with NYHA Class III at the time of CRT implantation

MADIT-CRT: Changes in Regional Strain from Baseline to 12 Months with Speckle Tracking

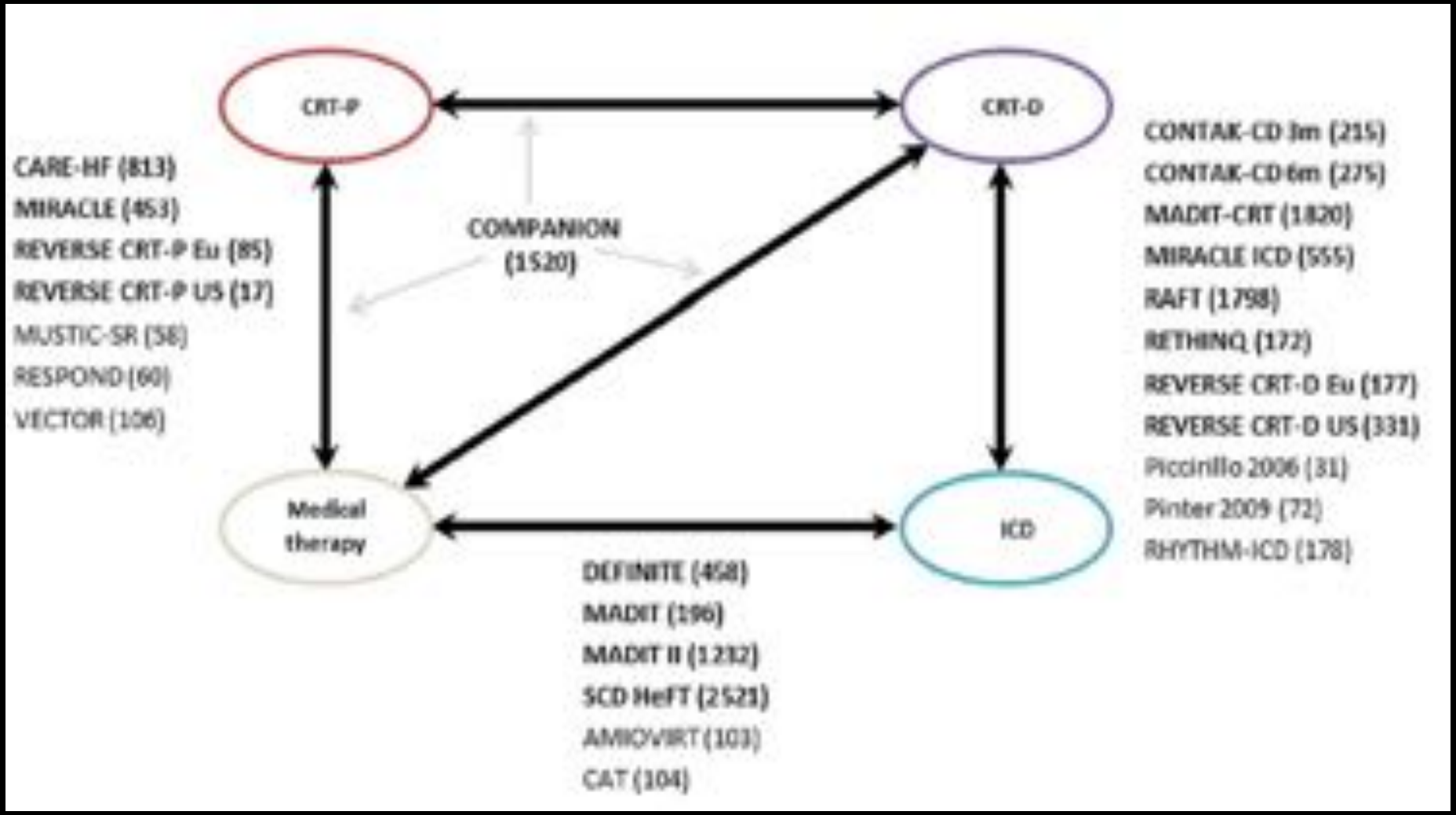


Baseline

12-Months

Slide provided by Dr. Scott Solomon, MADIT-CRT Echo Core Lab

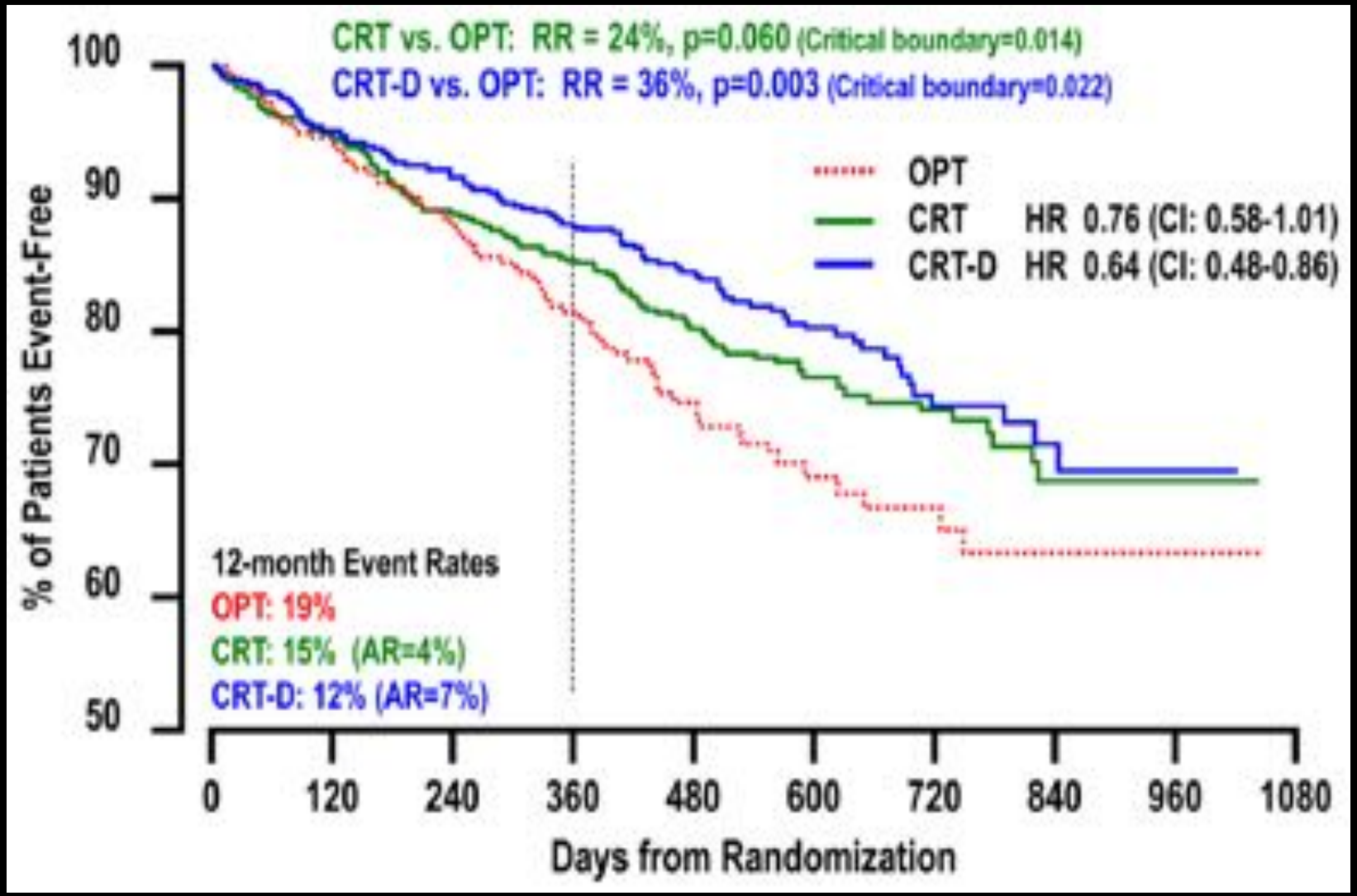
Available trial data for ICD, CRT-D and CRT-P



B. Woods et al. Heart 2015 doi:10.1136/heartjnl-2015-307634

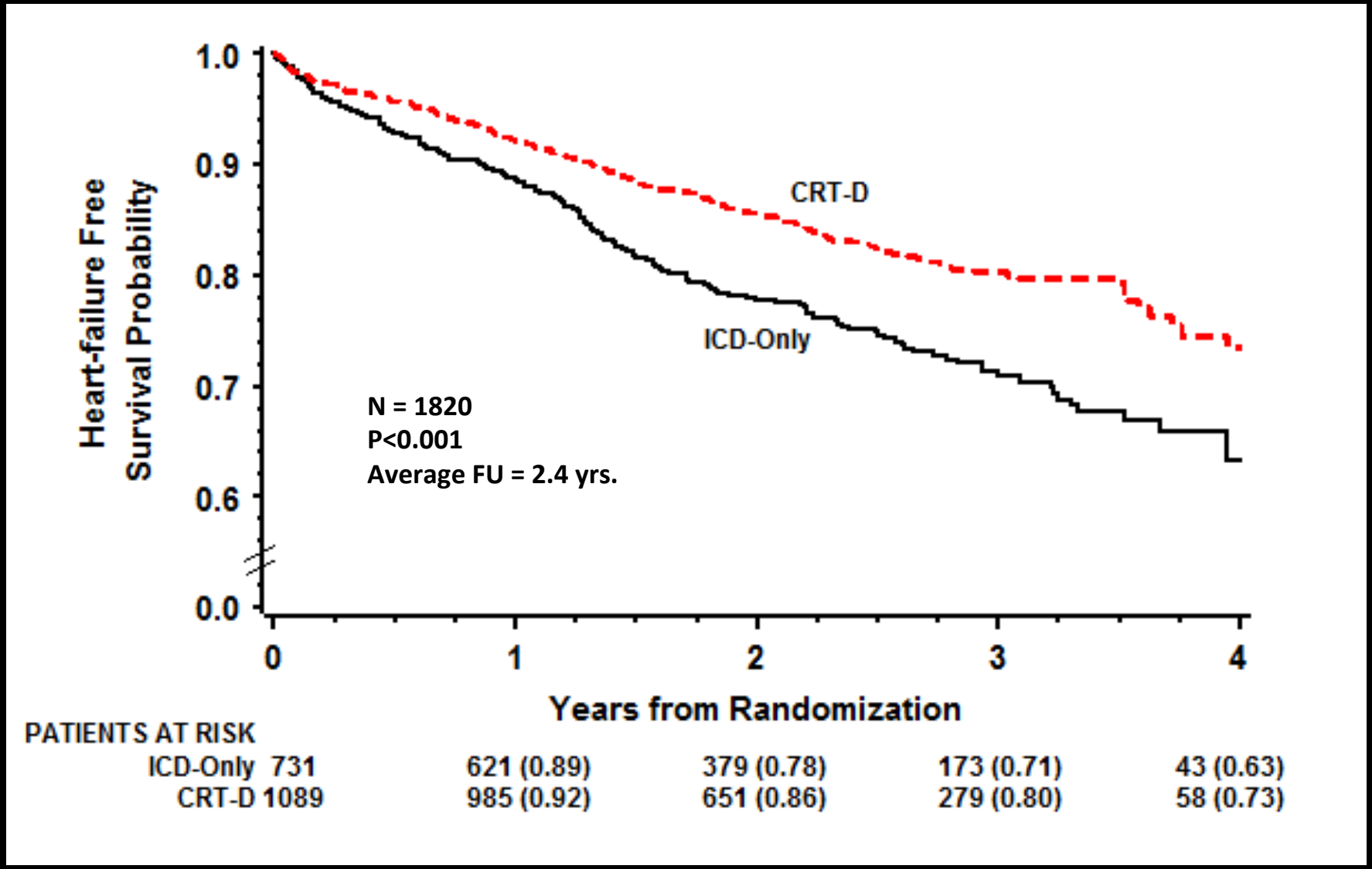
COMPANION

Secondary endpoint: All-Cause Mortality

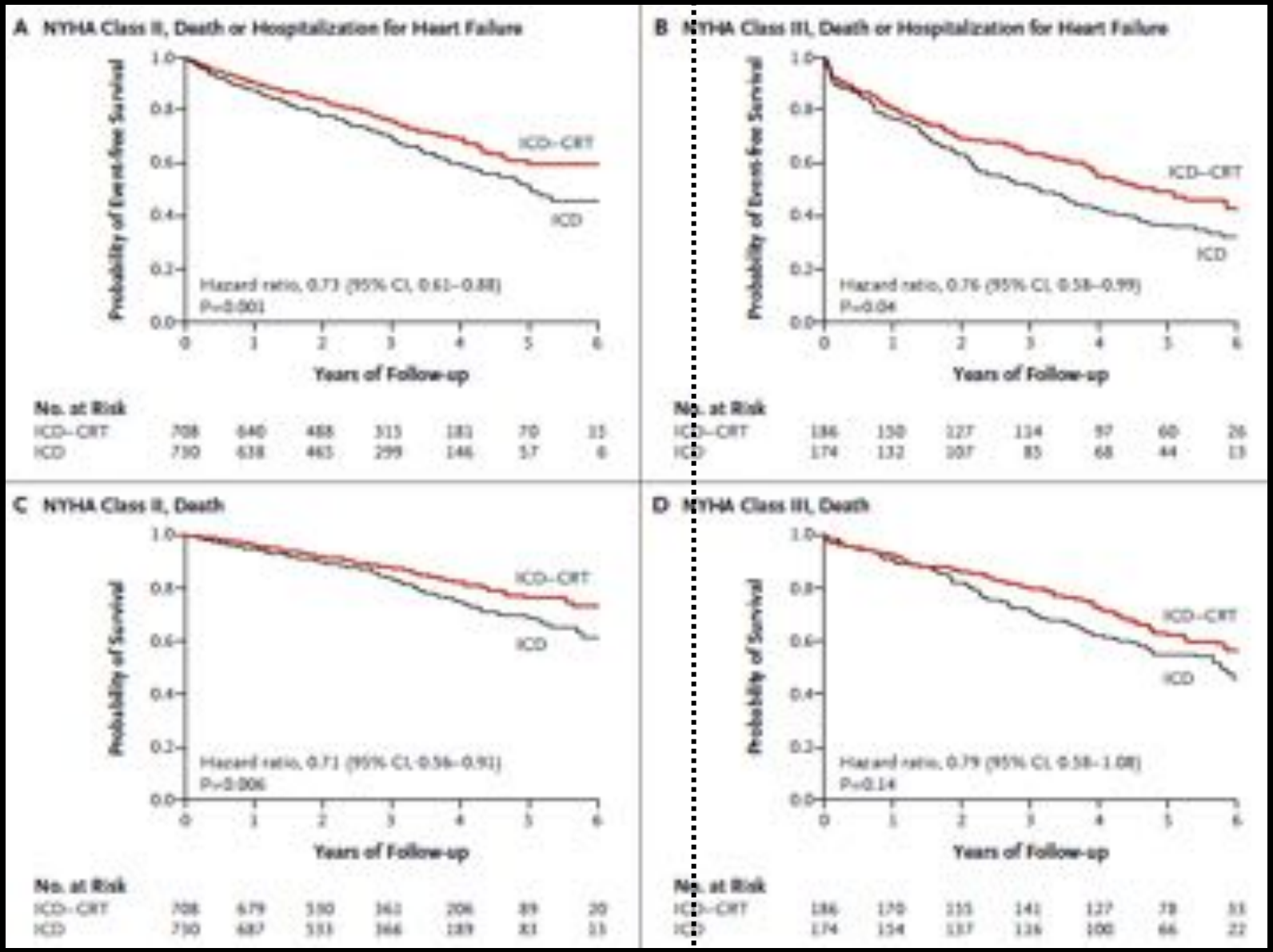


Bristow et al. NEJM 2004

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



AJ Moss, N Engl J Med 2009; 361: 1329-38



RAFT

ASL Tang et al. N Engl.J Med 2010;363: 2385-95

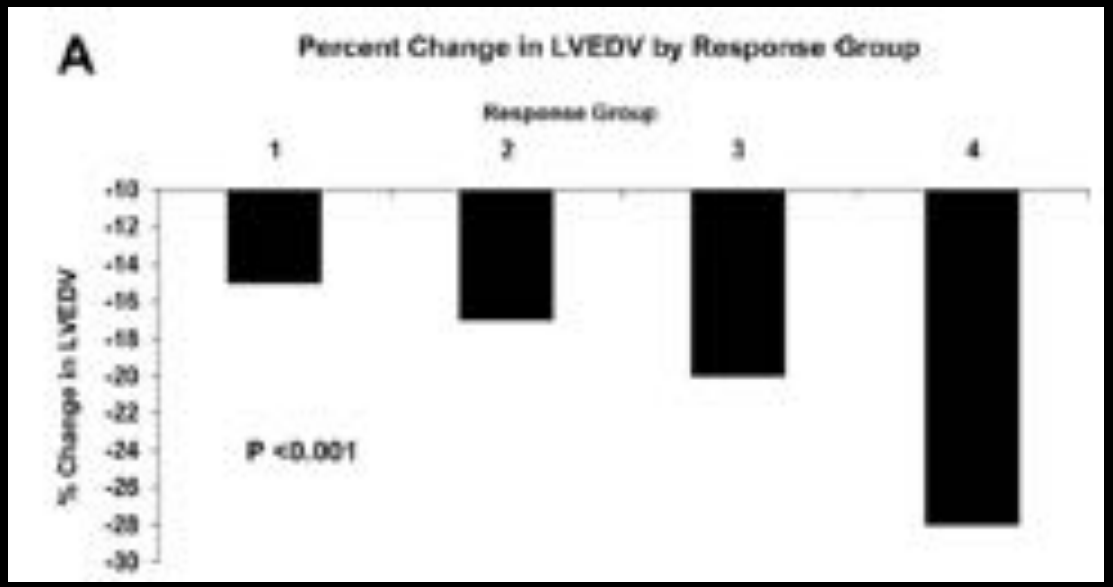
Predictors of response to CRT (MADIT-CRT)

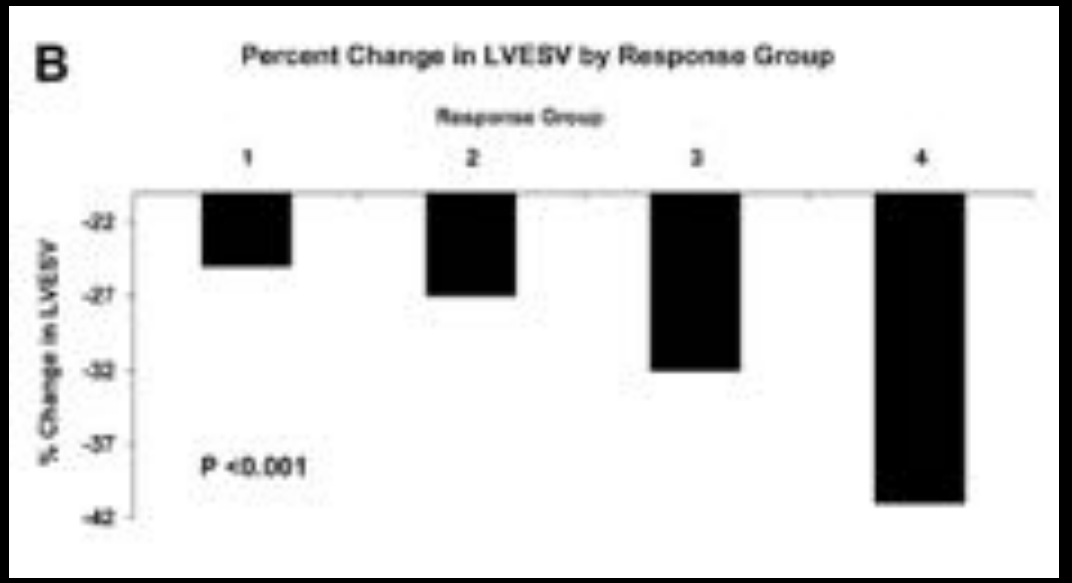
	High Response				Low Response				High vs Low*		
Risk Factor (Covariate)	Definition	n	Reduction (SD), %	>10% Reduction, %	Definition	n	Reduction (SD), %	>10% Reduction, %	Difference in Reduction (SE), %*	P	Score†
Sex	Women	275	−24 (11)	91	Men	814	−19 (11)	83	−2.9 (1.0)	0.003	2
CMP origin	Nonischemic	491	−24 (12)	90	Ischemic	598	−18 (10)	82	−4.2 (0.9)	<0.001	2
QRS	≥150 ms	688	−22 (12)	88	<150 ms	383	−18 (9)	79	−2.7 (0.9)	0.003	2
QRS pattern	LBBB	750	−22 (11)	88	Non-LBBB	321	−12 (10)	79	−3.4 (1.0)	<0.001	2
Prior HF hospitalization	Yes	493	−22 (12)	87	No	578	−19 (11)	82	−1.9 (0.8)	0.02	1
Baseline LVEDV	≥125 mL/m²	803	−21 (11)	88	<125 mL/m²	267	−18 (11)	83	−4.2 (1.1)	<0.001	2
Baseline LAV	<40 mL/m²	258	−23 (12)	87	≥40 mL/m²	811	−20 (11)	78	−5.6 (1.0)	<0.001	3

I. Goldenberg et al. Circulation 2011;124: 1527-36

Predictors of response to CRT

Average reduction in LVEDV / LVESV according to response categories





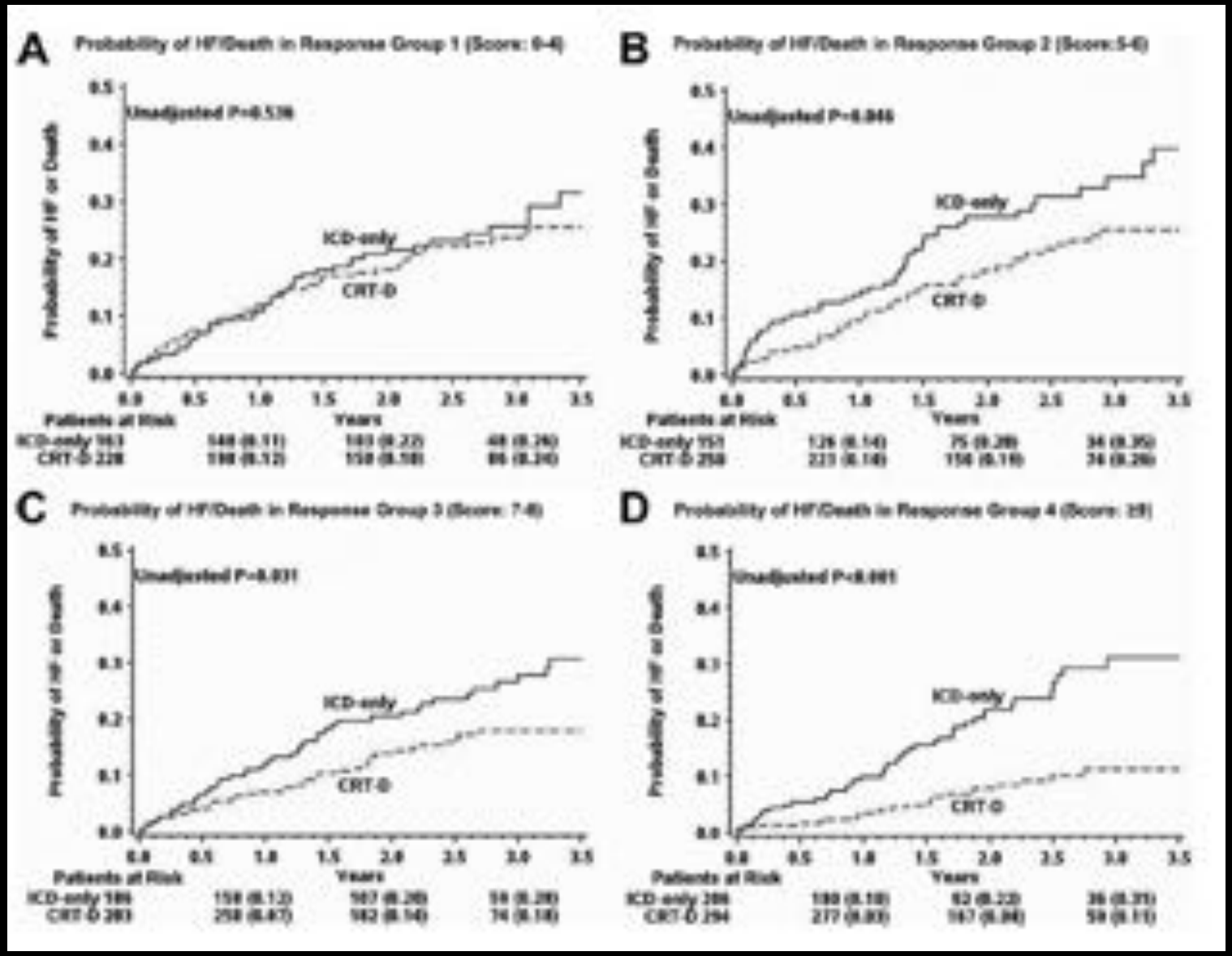
Predictors of response to CRT

Response Groups	Score	CRT-D vs ICD-Only Risk of HF or Death: HR	95% CI	P	P for Trend†
All patients (n=1761)	0–14	0.62	0.51–0.77	<0.001	NA
By response score quartile					
1 (n=391)	0–4	0.87	0.58–1.32	0.52	0.005
2 (n=401)	5–6	0.67	0.46–0.98	0.04	
3 (n=469)	7–8	0.64	0.43–0.97	0.03	
4 (n=500)‡	≥9	0.31	0.20–0.53	<0.001	
By individual response scores (per unit increment)		0.87§	0.81–0.96	<0.001	

I. Goldenberg et al. Circulation 2011;124: 1527-36

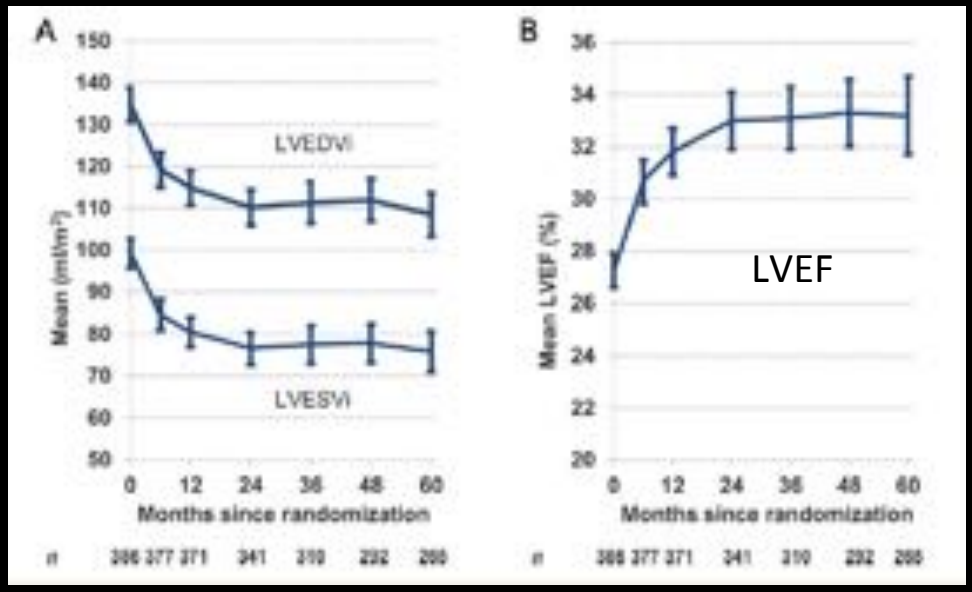
Predictors of response to CRT

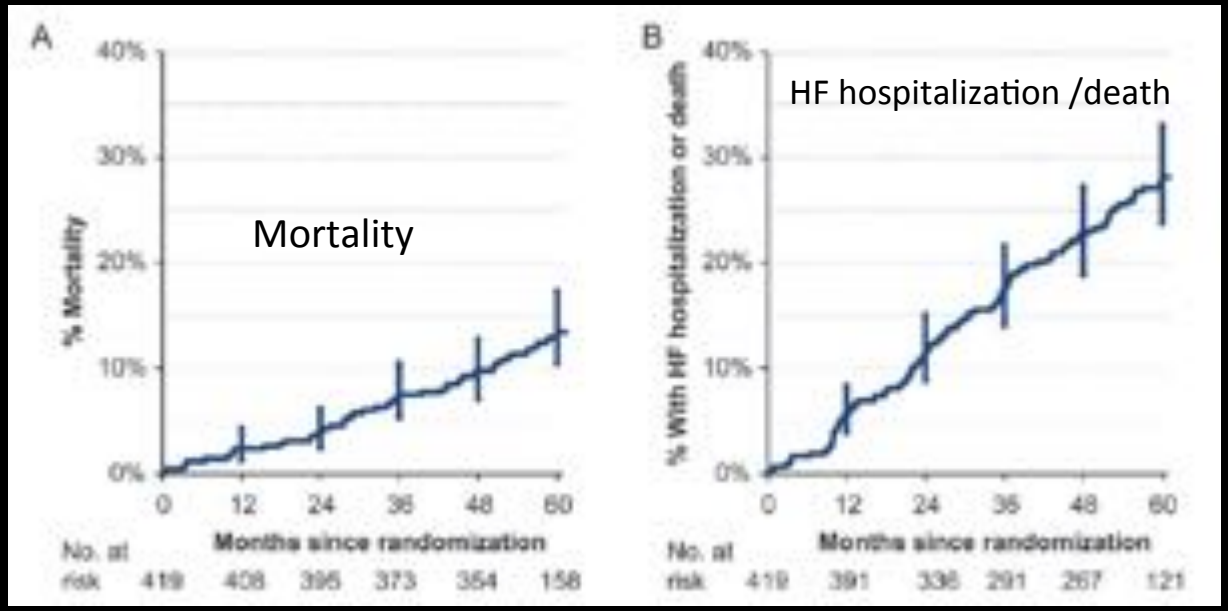
Cumulative probability of HF/Death in response score quartiles



I. Goldenberg et al. Circulation 2011;124: 1527-36

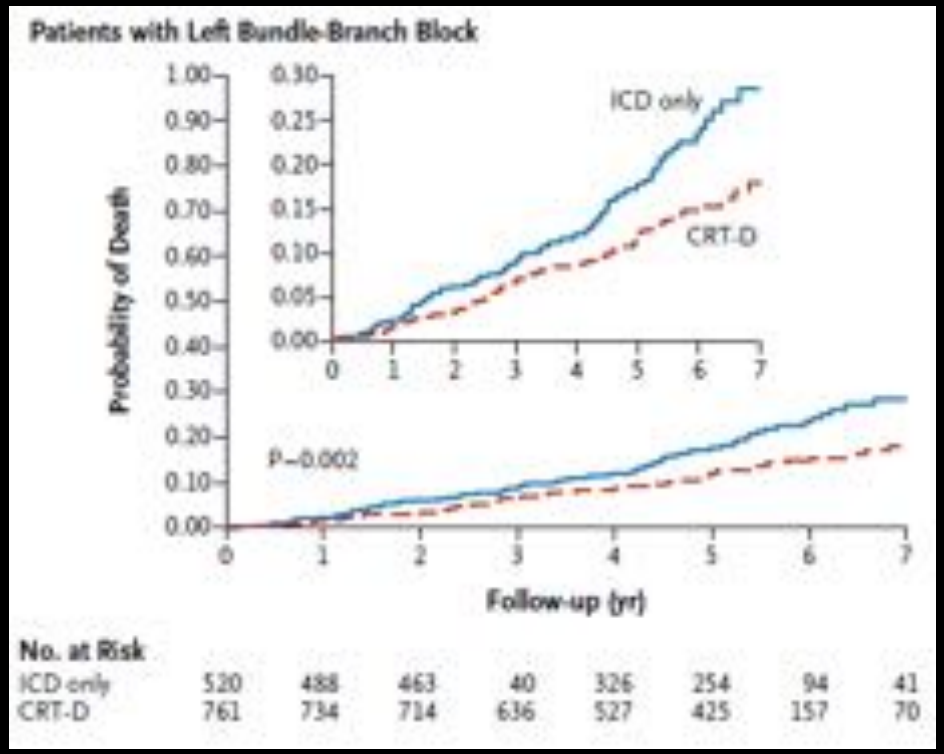
Long-term effect of CRT in mild heart failure after 5 years (REVERSE)





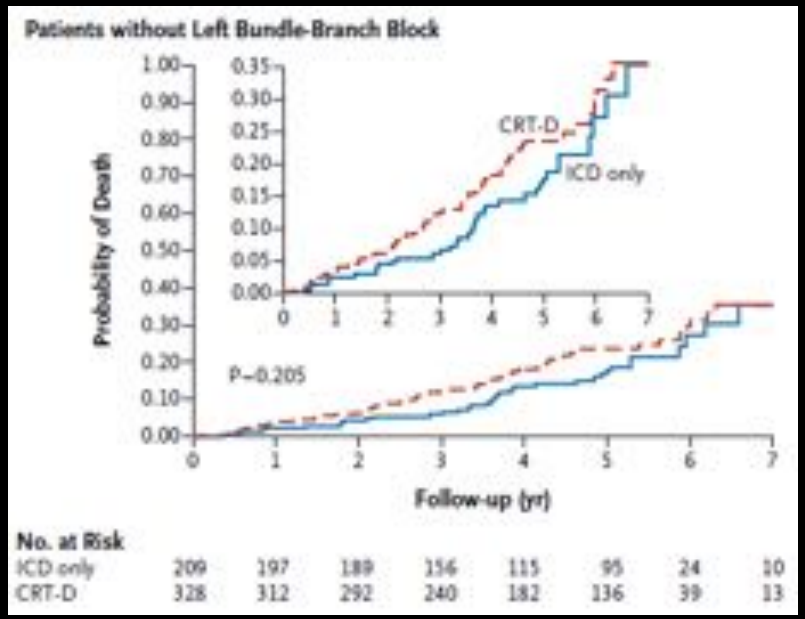
C. Linde et al. EHJ 2013; 34:2592-99

Long-term survival in pts with CRT-D vs ICD only (MADIT-CRT)



LBBB

Non-LBBB



I. Goldenberg et al.
New Engl J Med 2014; 370:1694-701

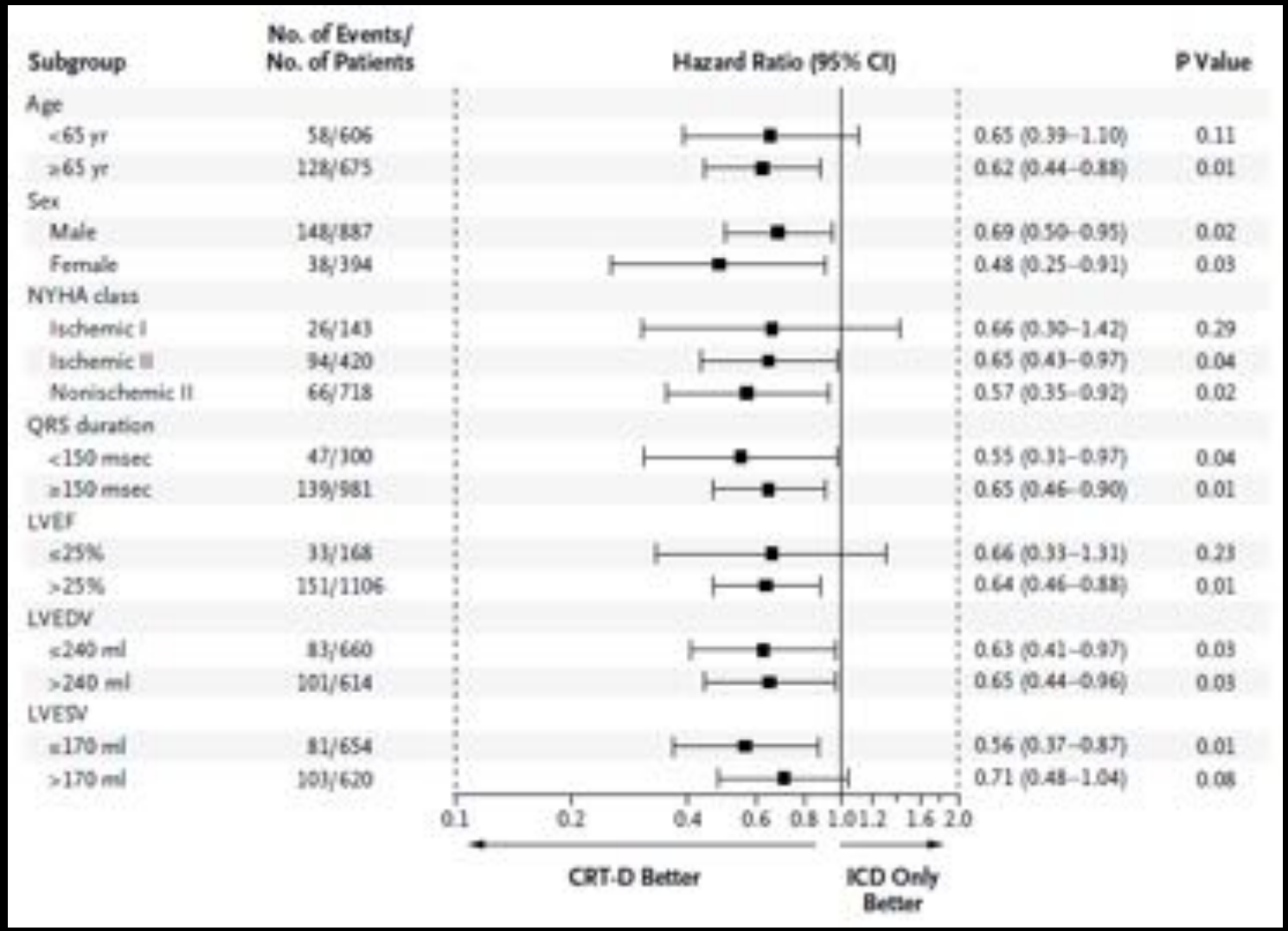
MADIT-CRT Long-term Follow-up

Endpoints LBBB versus Non-LBBB

End Point	No. of Events	No. of Patients	Left Bundle-Branch Block		Non–Left Bundle-Branch Block		P Value for Interaction*
			Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	
Death from any cause							
Unadjusted analysis	292	1818	0.63 (0.47–0.84)	0.002	1.31 (0.87–1.96)	0.19	0.004
Adjusted analysis†	267	1681	0.59 (0.43–0.80)	<0.001	1.57 (1.03–2.39)	0.04	<0.001
Nonfatal heart-failure event							
Unadjusted analysis	442	1818	0.42 (0.33–0.52)	<0.001	1.10 (0.79–1.53)	0.59	<0.001
Adjusted analysis†	405	1681	0.38 (0.30–0.48)	<0.001	1.13 (0.80–1.60)	0.48	<0.001
Nonfatal heart-failure event or death							
Unadjusted analysis	577	1818	0.50 (0.41–0.61)	<0.001	1.21 (0.90–1.63)	0.21	<0.001
Adjusted analysis†	530	1681	0.45 (0.37–0.56)	<0.001	1.27 (0.94–1.73)	0.12	<0.001

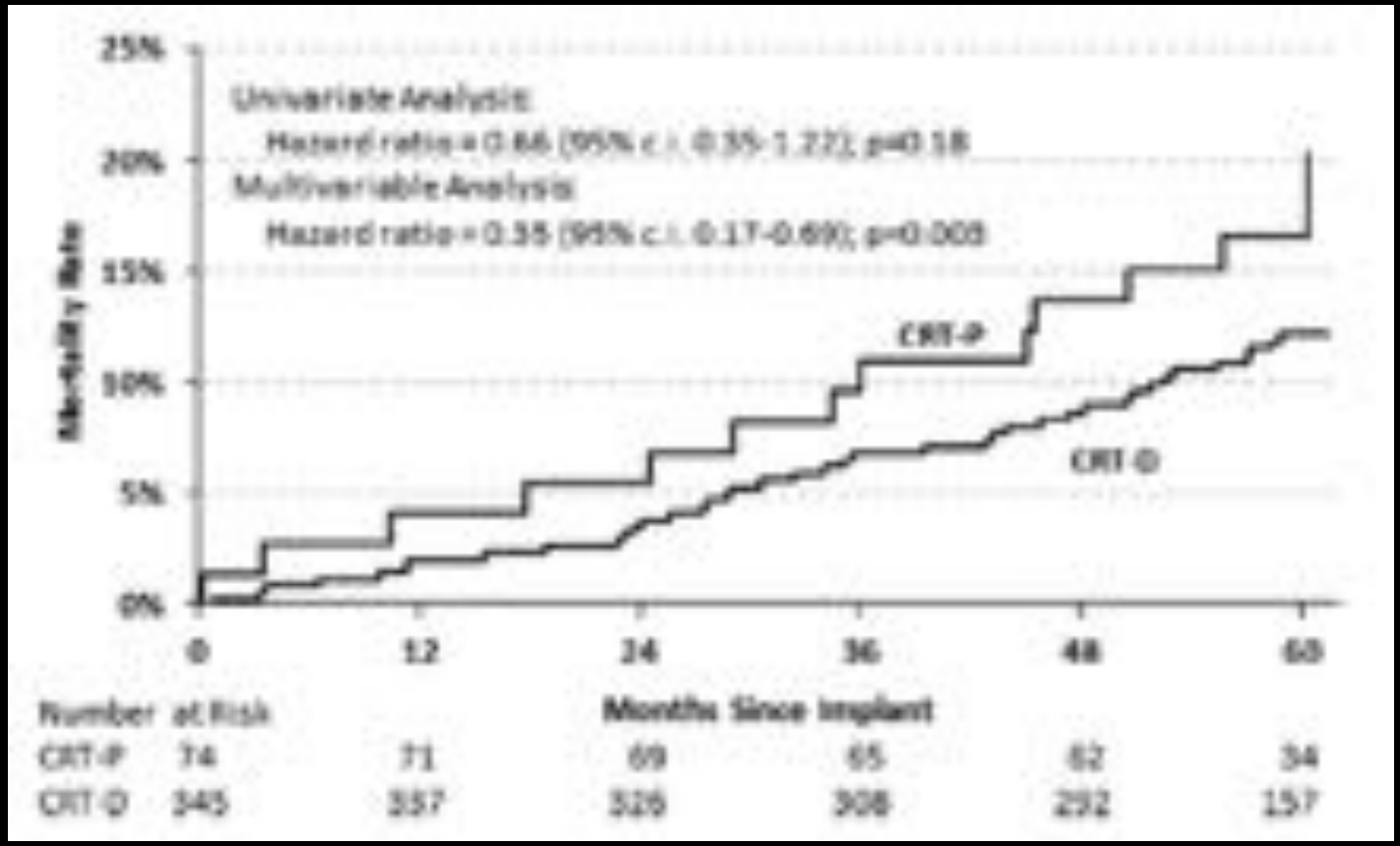
I. Goldenberg et al.
New Engl J Med 2014; 370:1694-701

Risk of death in patients with LBBB



I. Goldenberg et al.
New Engl J Med 2014; 370:1694-701

REVERSE Long-term Follow-up
Mortality > 5years



Cardiac deaths

	CRT-P	CRT-D
SCD	5%	2%
Non-sudden	4%	4%

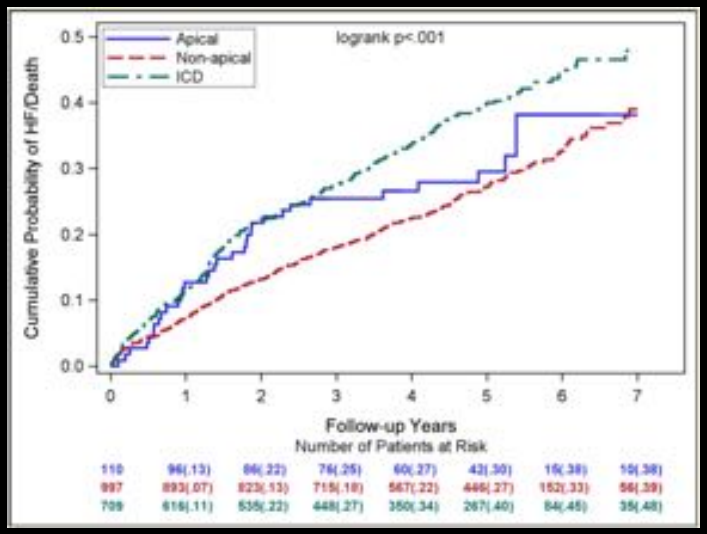
MR Gold et al. Circ Arrhythm Electrophysiol 2013; 6:1163-68

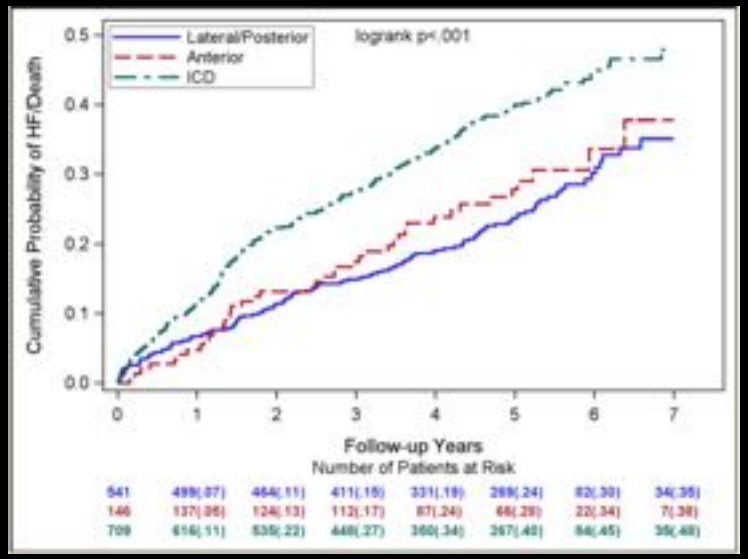
REVERSE Long-term follow-up data
Mortality >5 years
(multivariable Analysis)

Baseline Parameters	Units/Level	Hazard Ratio	P Value
Device type	CRT-D	0.35	0.003
Age	Per 10 y	1.33	0.08
LVEF	Per 10%	0.92	0.74
QRS duration	Per 10 ms	0.81	0.008
LVESVi	Per 10 mL/m²	1.17	0.0003
Sex	Female	0.07	0.009
Diabetes mellitus	Yes	1.04	0.90
Ischemic	Yes	1.78	0.15
NYHA class	I	0.62	0.57
LBBB	Yes	0.66	0.22

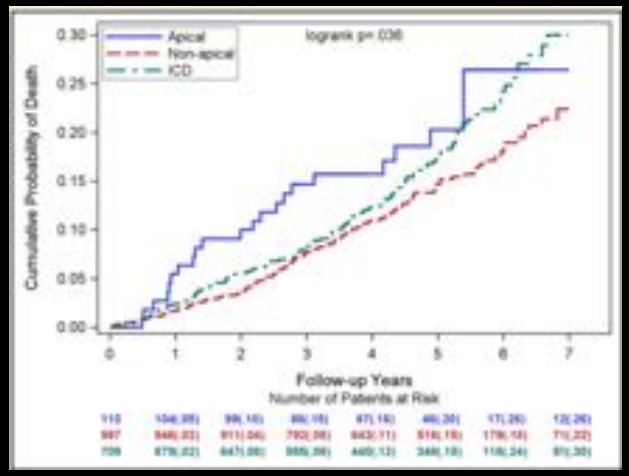
MR Gold et al. Circ Arrhythm Electrophysiol 2013; 6:1163-68

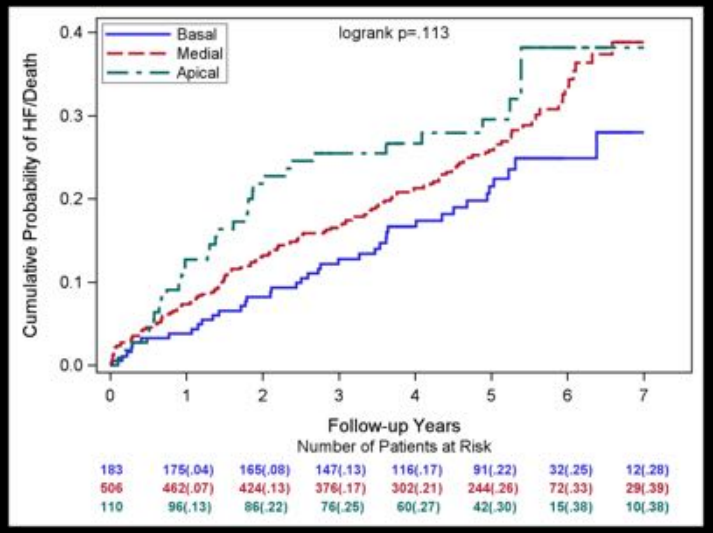
Long-term outcome related to LV-lead position





Death alone



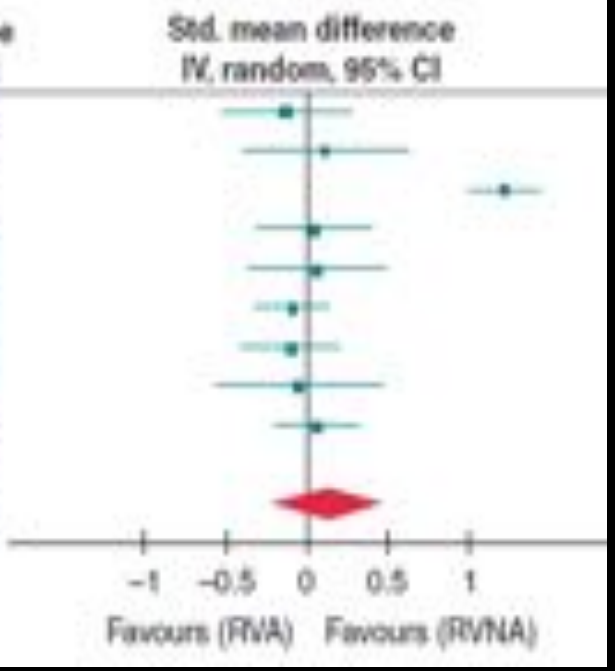


A. Kosztin et al. Circ Arrhythm 2014

Where to place the RV-lead in CRT patients ?

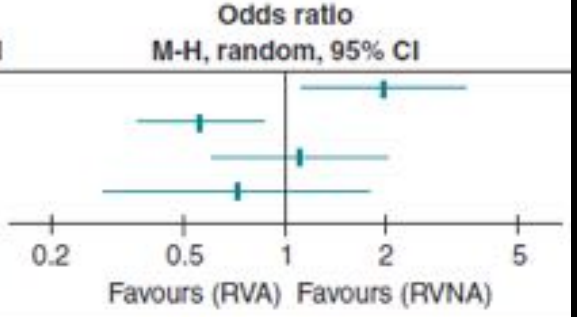
Study or subgroup	RVA Mean	RVA SD	RVA Total	RVNA Mean	RVNA SD	RVNA Total	Weight	Std. mean difference IV, random, 95% CI
Bulava (2009)	−57	92.63	82	−46	54.45	35	10.9%	−0.13 [−0.53, 0.26]
Haghjoo (2009)	−40	37	50	−44	34	23	10.2%	−0.11 [−0.38, 0.60]
Kaitani (2012)	−15	2.7	284	−18.6	3.4	142	11.9%	1.22 [1.00, 1.44]
Khan (2011)	−33	90.43	76	−37	80.26	55	11.2%	0.05 [−0.30, 0.39]
Kristiansen (2012)	−36	66.22	43	−40	82.76	42	10.7%	0.05 [−0.37, 0.48]
Kutyifa (2013)	−34.85	21.27	656	−32.99	16.26	86	11.9%	−0.09 [−0.31, 0.14]
Leclercq (2014)	−29.3	44	92	−25.3	39	90	11.5%	−0.10 [−0.39, 0.20]
Ronn (2011)	−18	50	28	−15.7	39	30	10.0%	−0.05 [−0.57, 0.46]
Thebault (2012)	−18.2	30.4	197	−19.9	26.2	93	11.8%	0.06 [−0.19, 0.30]
Total (95% CI)			1508			596	100.0%	**0.13 [−0.24, 0.50]**

Heterogeneity: $\tau^2 = 0.29$; $\chi^2 = 99.84$, $df = 8 (P < 0.00001)$; $I^2 = 92\%$
Test for overall effect: $Z = 0.70$ $(P = 0.48)$



Changes in LVESV

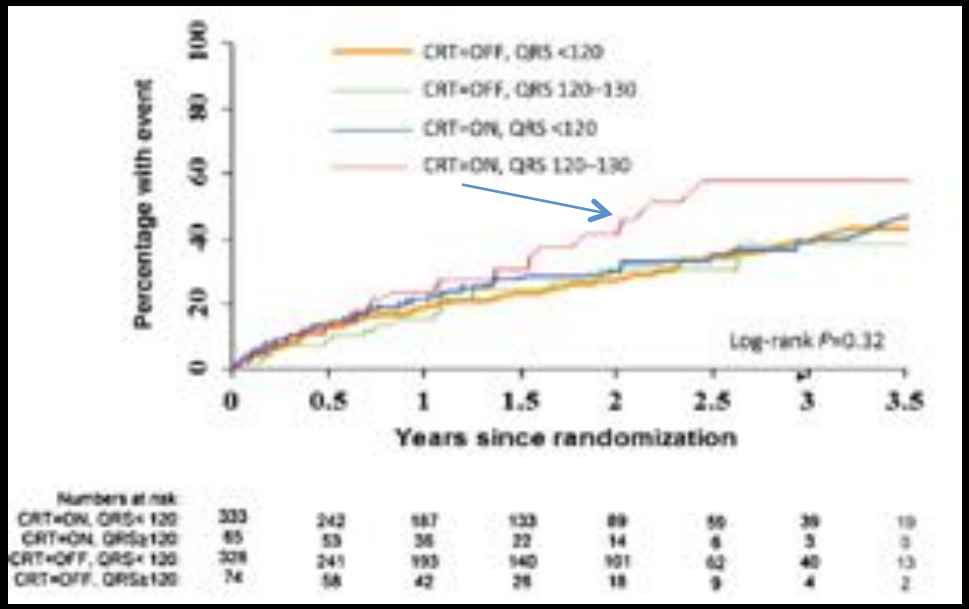
Study or subgroup	RVA Events	RVA Total	RVNA Events	RVNA Total	Weight	Odds ratio M-H, random, 95% CI
Jastrzebski 2013	32	57	120	305		1.97 [1.11, 3.49]
Kaitani 2012	74	284	55	142		0.56 [0.36, 0.86]
Kutyifa 2013	116	656	14	86		1.10 [0.60, 2.03]
Thebault 2012	13	237	8	108		0.73 [0.29, 1.81]

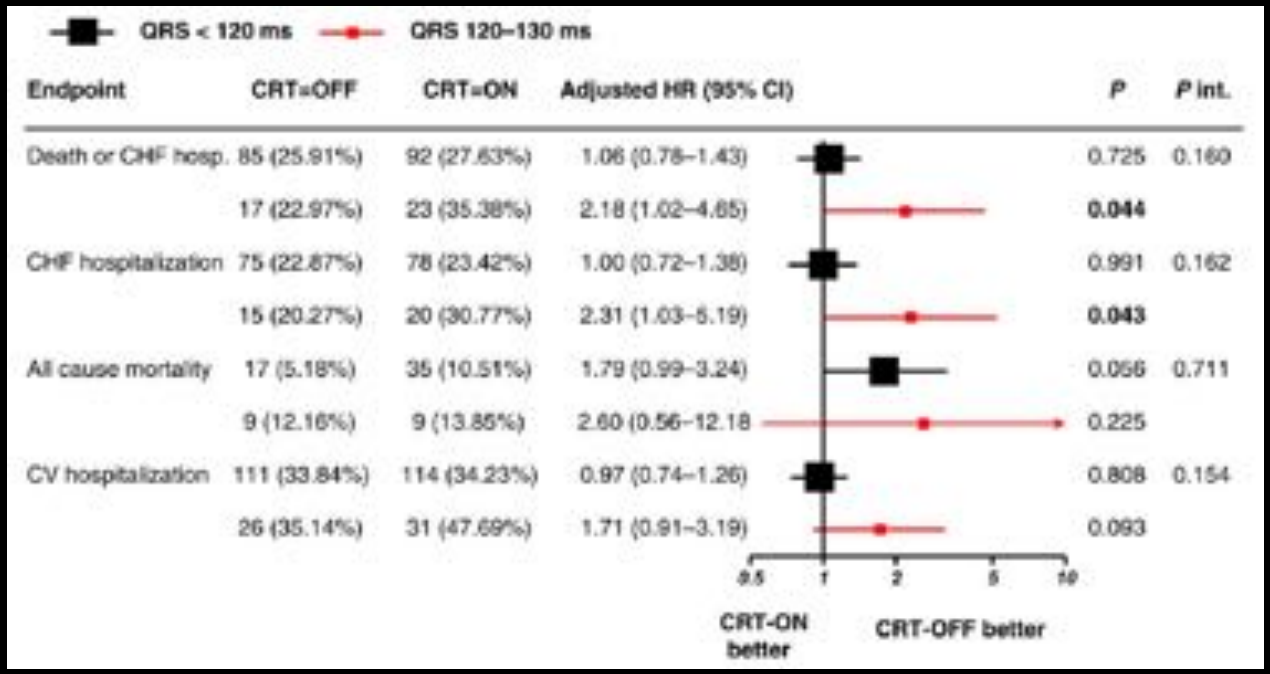


All-cause mortality and CV hospitalization

T.A. Zografos et al. Europace 2015 doi:10.1093/europace/euv048

Various QRS durations in ECHO-CRT

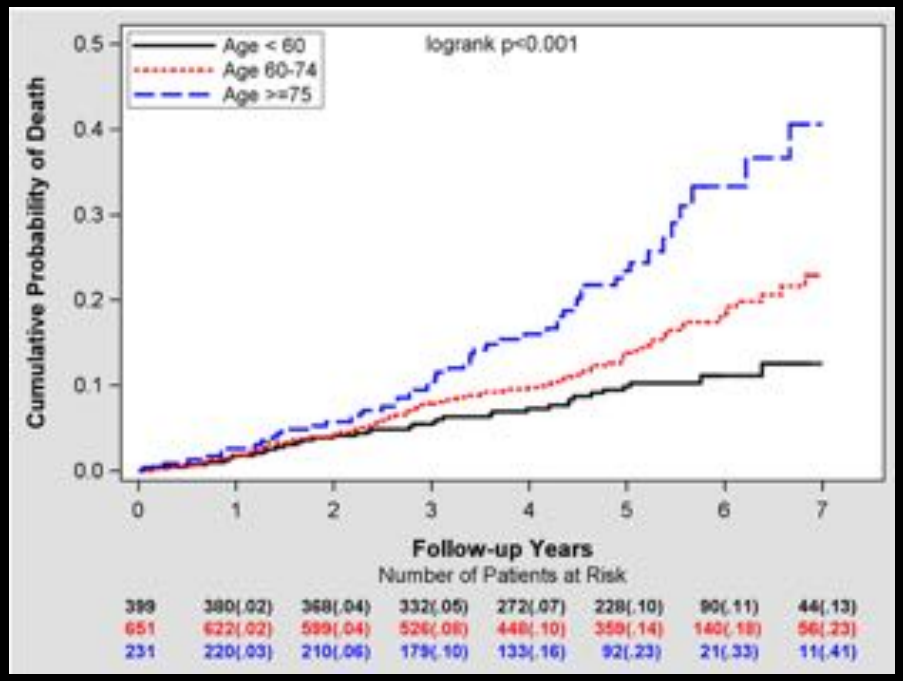




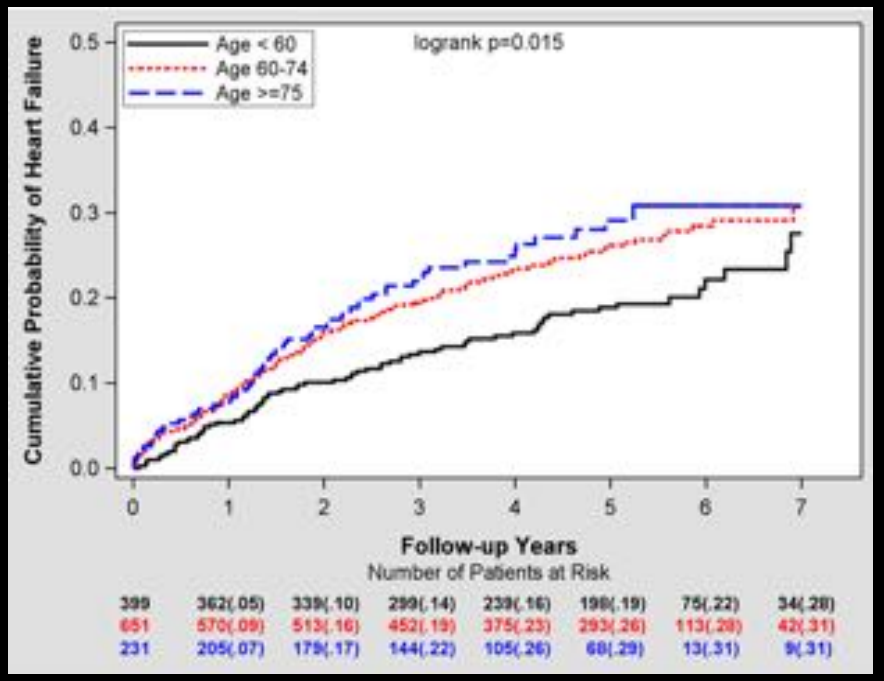
J. Steffel et al. EHJ 2015; 36:1983-89

Long-term Follow-up MADIT-CRT with LBBB patients

Does age matter ?



All cause death

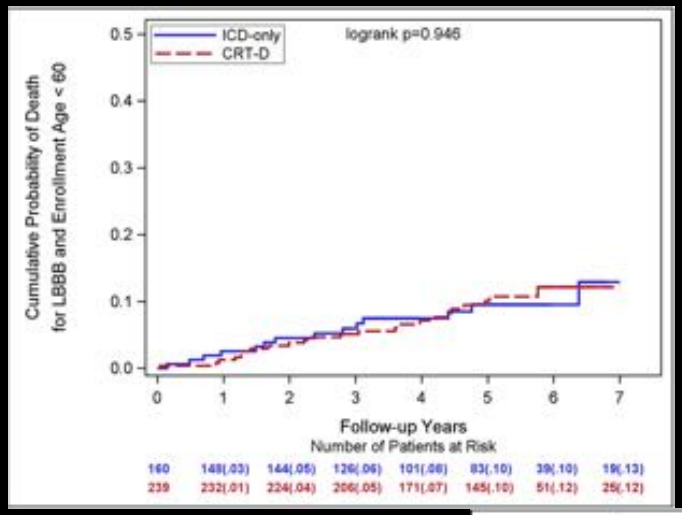


Heart Failure

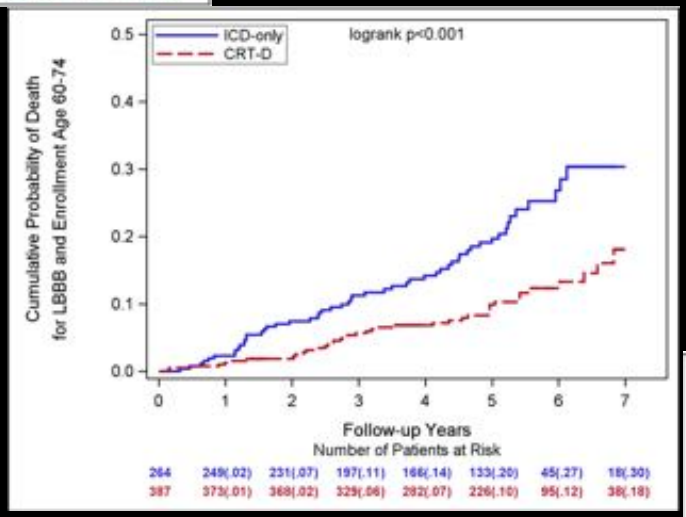
S. Thomas et al. J Cardiac Fail 2015 9 online

Long-term Follow-up MADIT-CRT with LBBB patients

Probability of all cause death

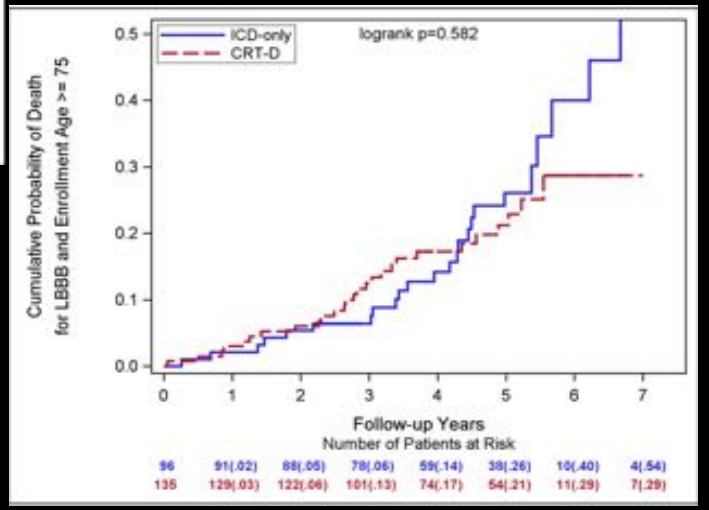


< 60 years



60-74 years

≥75 years



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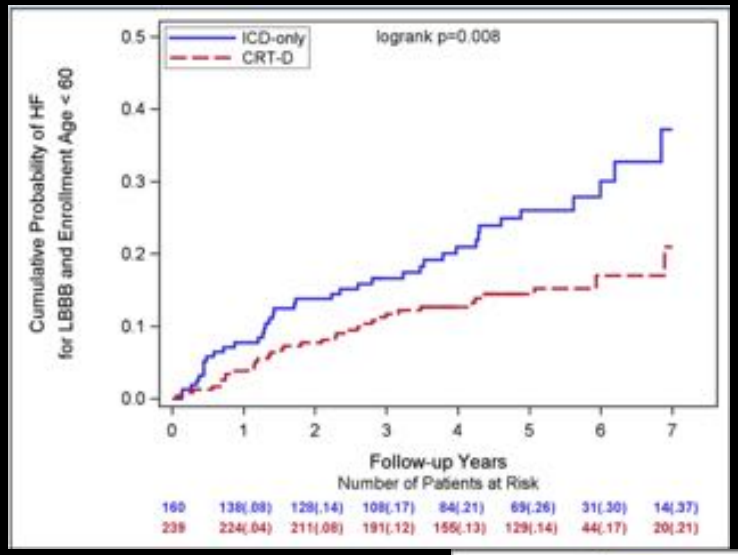
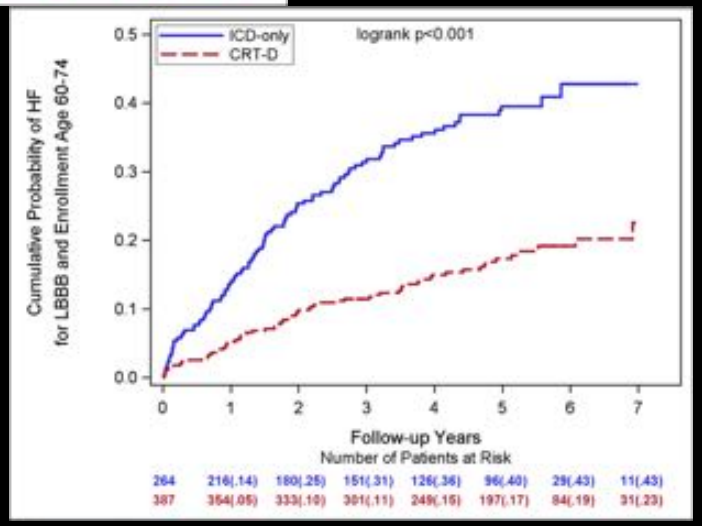
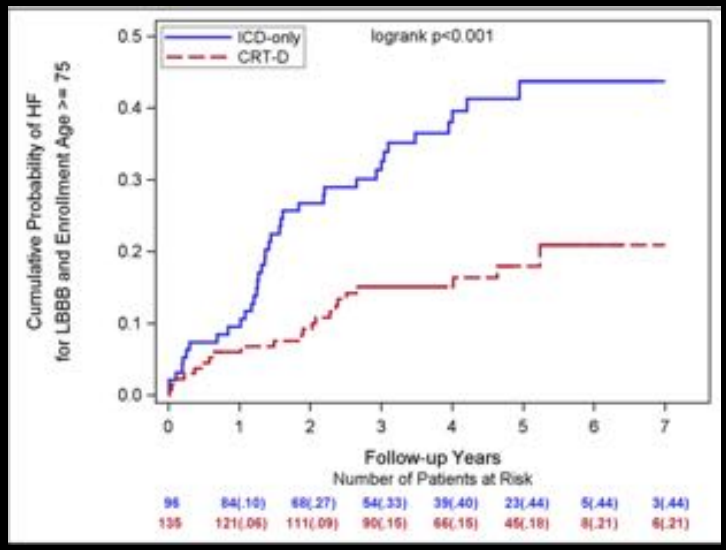
Long-term Follow-up MADIT-CRT with LBBB patients

Probability of Heart Failure







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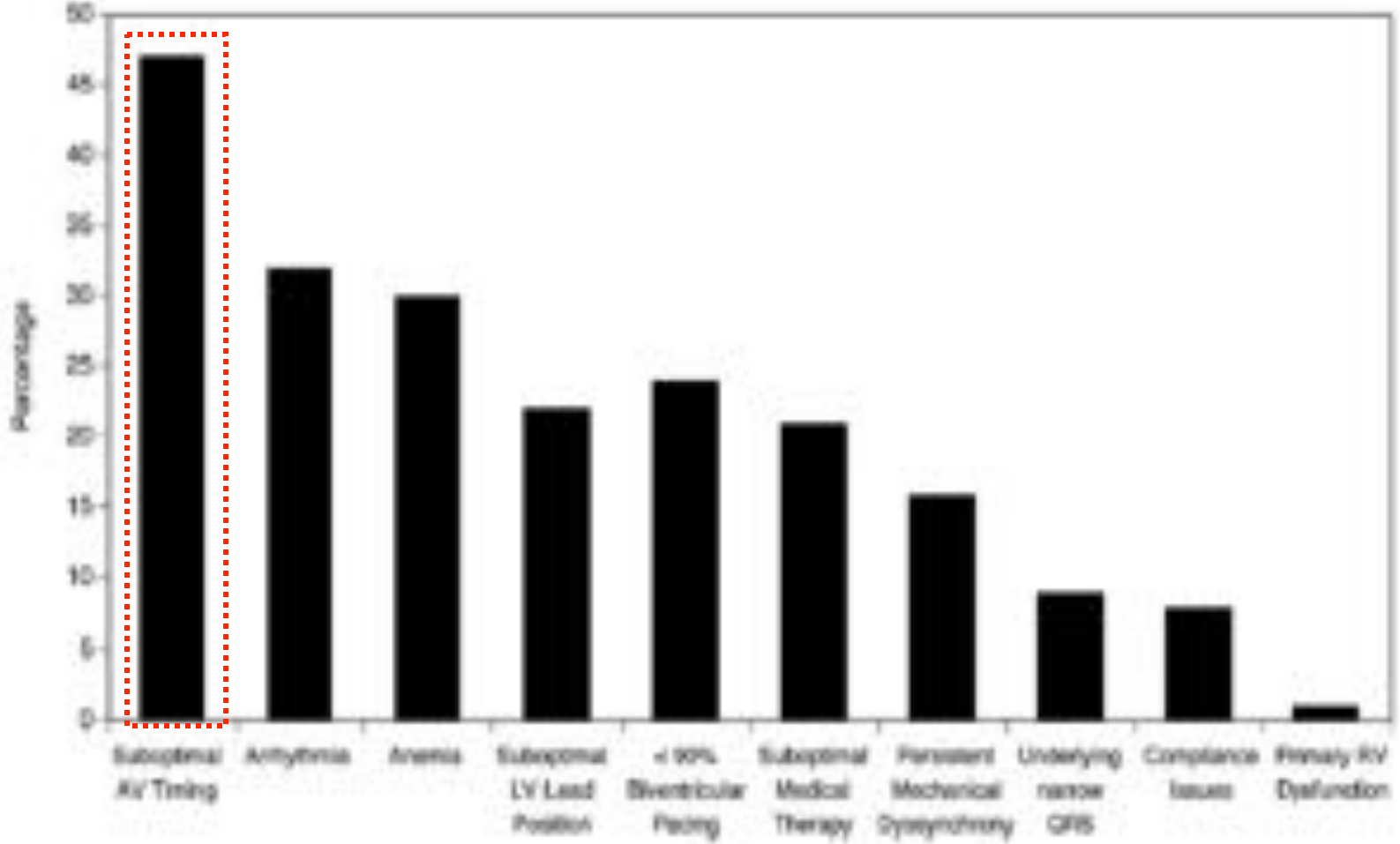
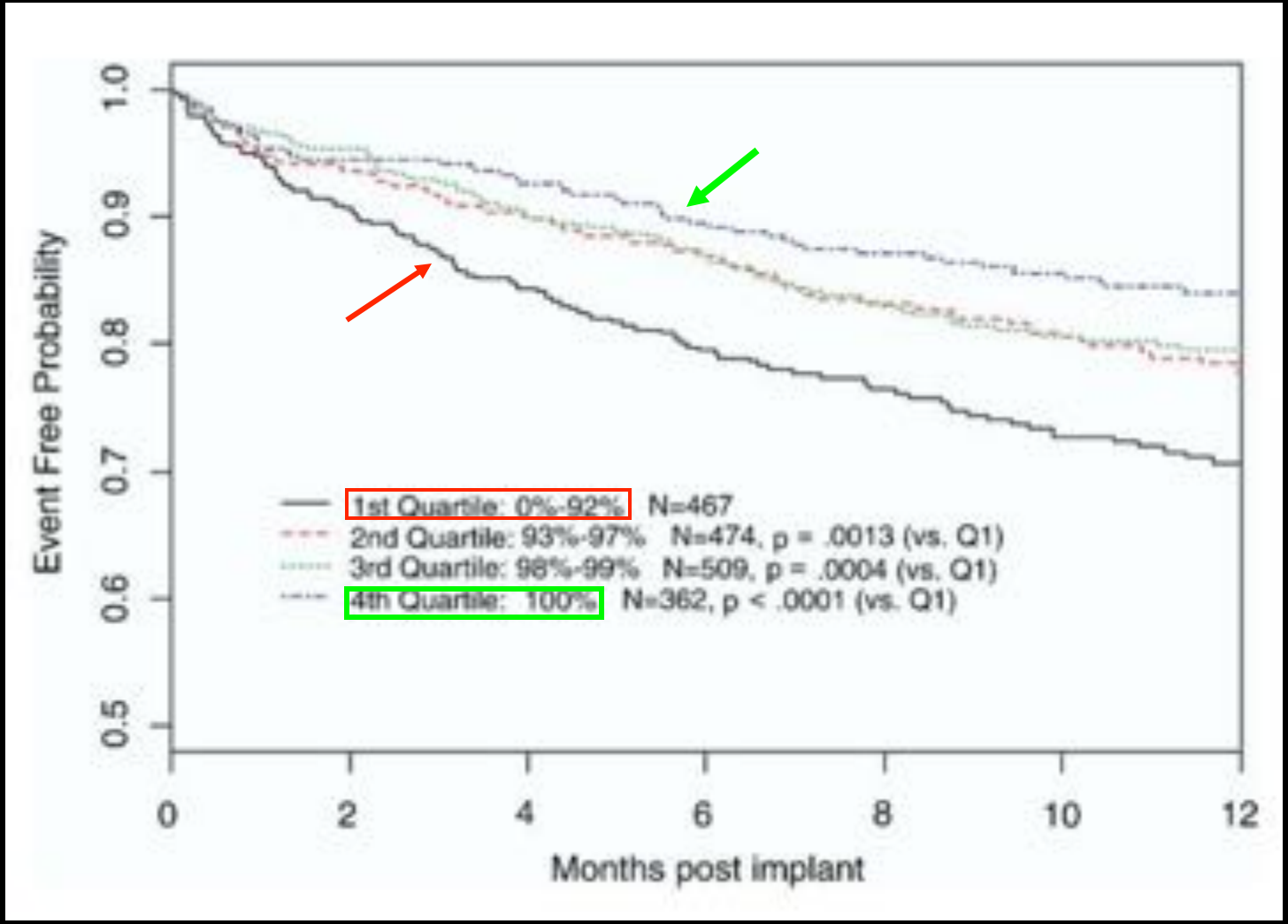
Reasons for “suboptimal” response to CRT



Mullens W, et al. JACC 2009;53: 765-73

Importance of *complete* bi-ventricular pacing with CRT



Survival free from heart failure hospitalization and overall mortality

Koplan BA, et al. JACC 2009; 53: 355-60

Quadripolar LV leads for CRT

Is this the solution?

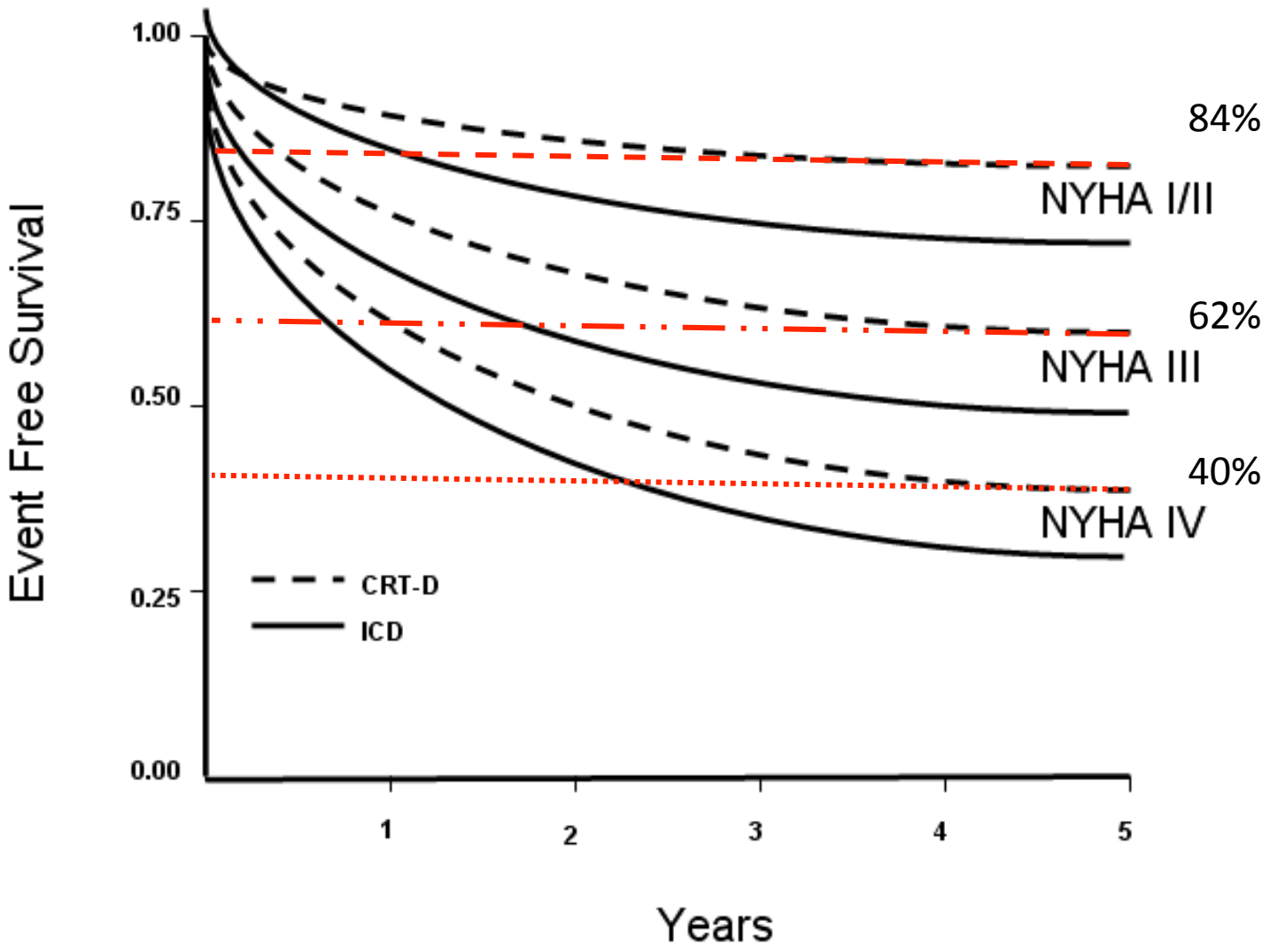
High stimulation thresholds and PNS ?

MS Parahuleva et al. Clin Med. Insights: Cardiology 2011; 5: 45-47

CRT-D/P the earlier the better !

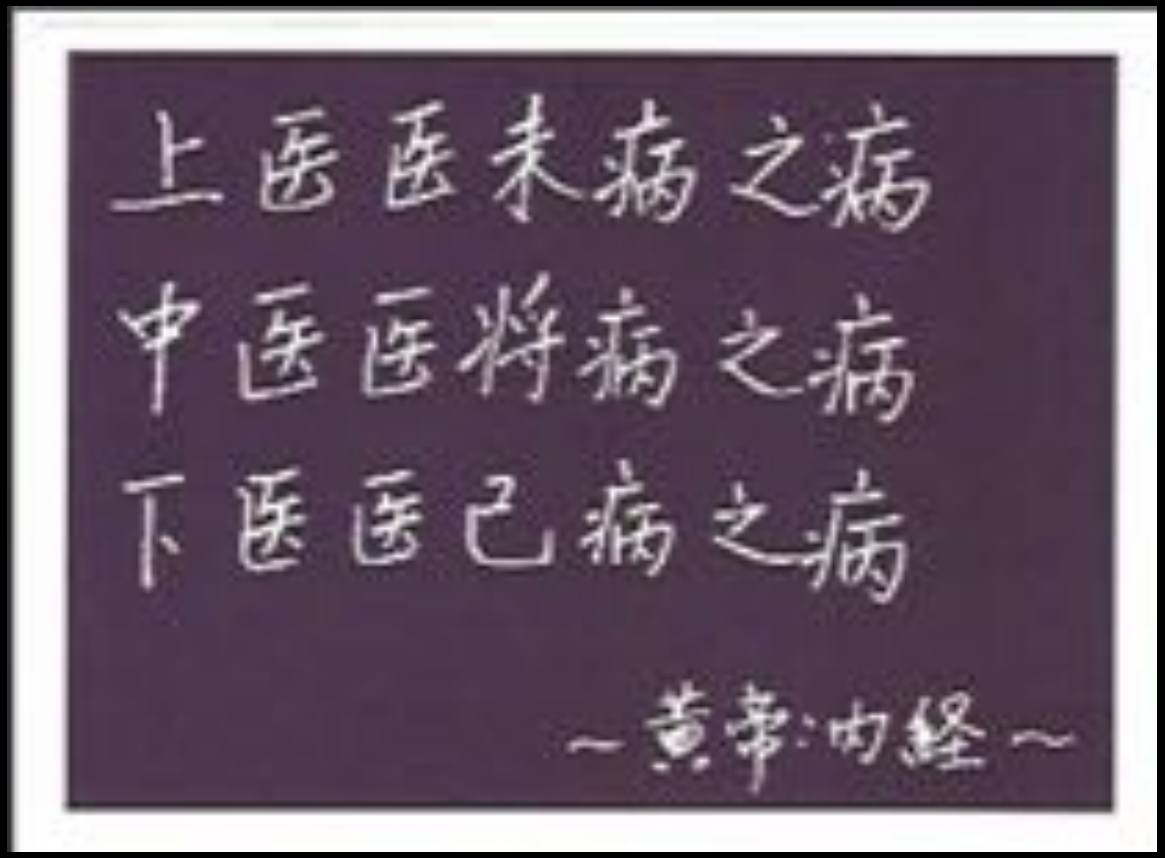
	Overall mortality / 3 years	per year
NYHA III/IV		
• COMPANION	30%	12%
• CARE-HF	24%	7.9%
NYHA I/II		
• MADIT-CRT	8.5%	3%
• RAFT	10%	

Hypothetical Survival Curves (CRT-D (P)



Improvement of long-term CRT

- Selection of the predictable CRT responders
- Application of CRT in an early status of mild heart failure ("the earlier the better")
- Optimization (Adjustment) of the AV delay to improve LV diastolic filling and to reduce mitral regurgitation
- Reduction of LA remodeling to reduce incidence of AF
- Reduction of LV lead complications (8%-10%)
- Role of multi-polar lead LV pacing ?
- Role of tele-monitoring for CRT patients?



Huang Dee: Nai Ching,
Yellow Emperor's Text Book of Medicine,
2600 BCE - the first chinese medical text

"Good doctors prevent the disease,
Mediocre doctors treat the disease prior to the disaster
Poor doctors treat the disaster"