QRS Morphology and Duration - Where are we in 2015?

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CONFLICT OF INTEREST TO DECLARE

Research Grants:

Boston Scientific
Zoll Inc.
Gilead Sciences

Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events

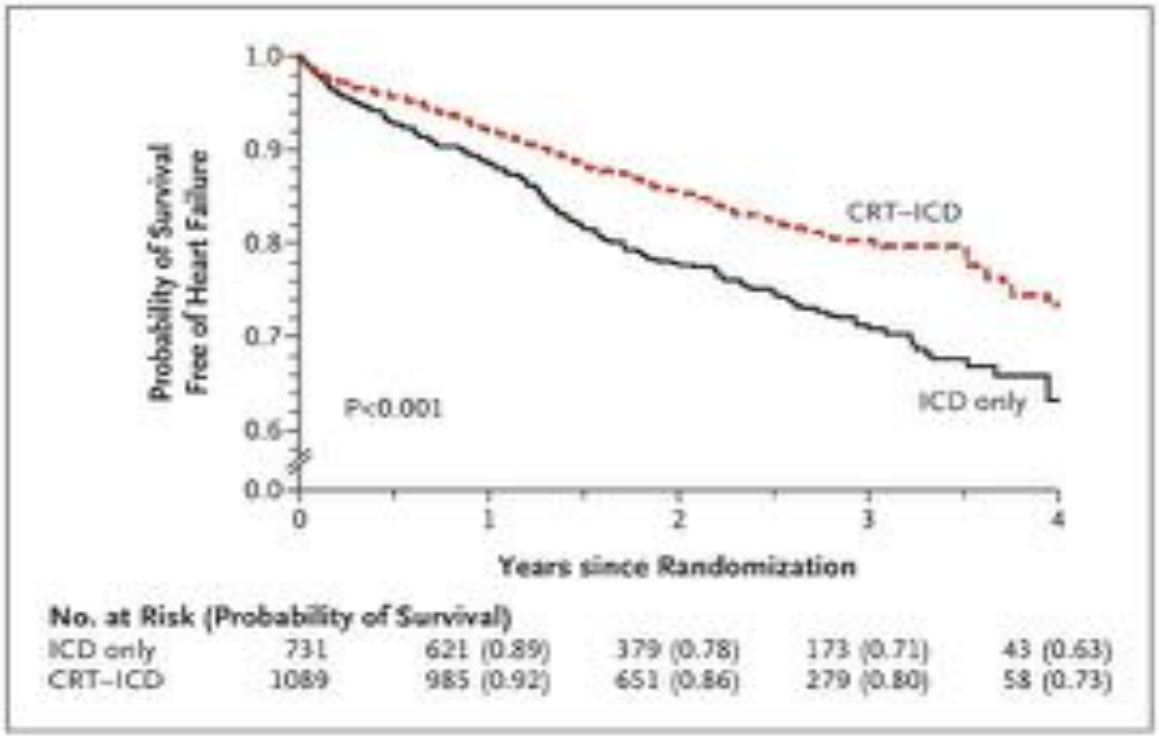
Arthur J. Moss, M.D., W. Jackson Hall, Ph.D., David S. Cannom, M.D., Helmut Klein, M.D., Mary W. Brown, M.S., James P. Daubert, M.D., N.A. Mark Estes III, M.D., Elyse Foster, M.D., Henry Greenberg, M.D., Steven L. Higgins, M.D., Marc A. Pfeffer, M.D., Ph.D., Scott D. Solomon, M.D., David Wilber, M.D., and Wojciech Zareba, M.D., Ph.D., for the MADIT-CRT Trial Investigators*

ICM NYHA I/II and NICM NYHA II
EF ≤ 0.30; QRS ≥0.13sec

Randomization
N=1,820

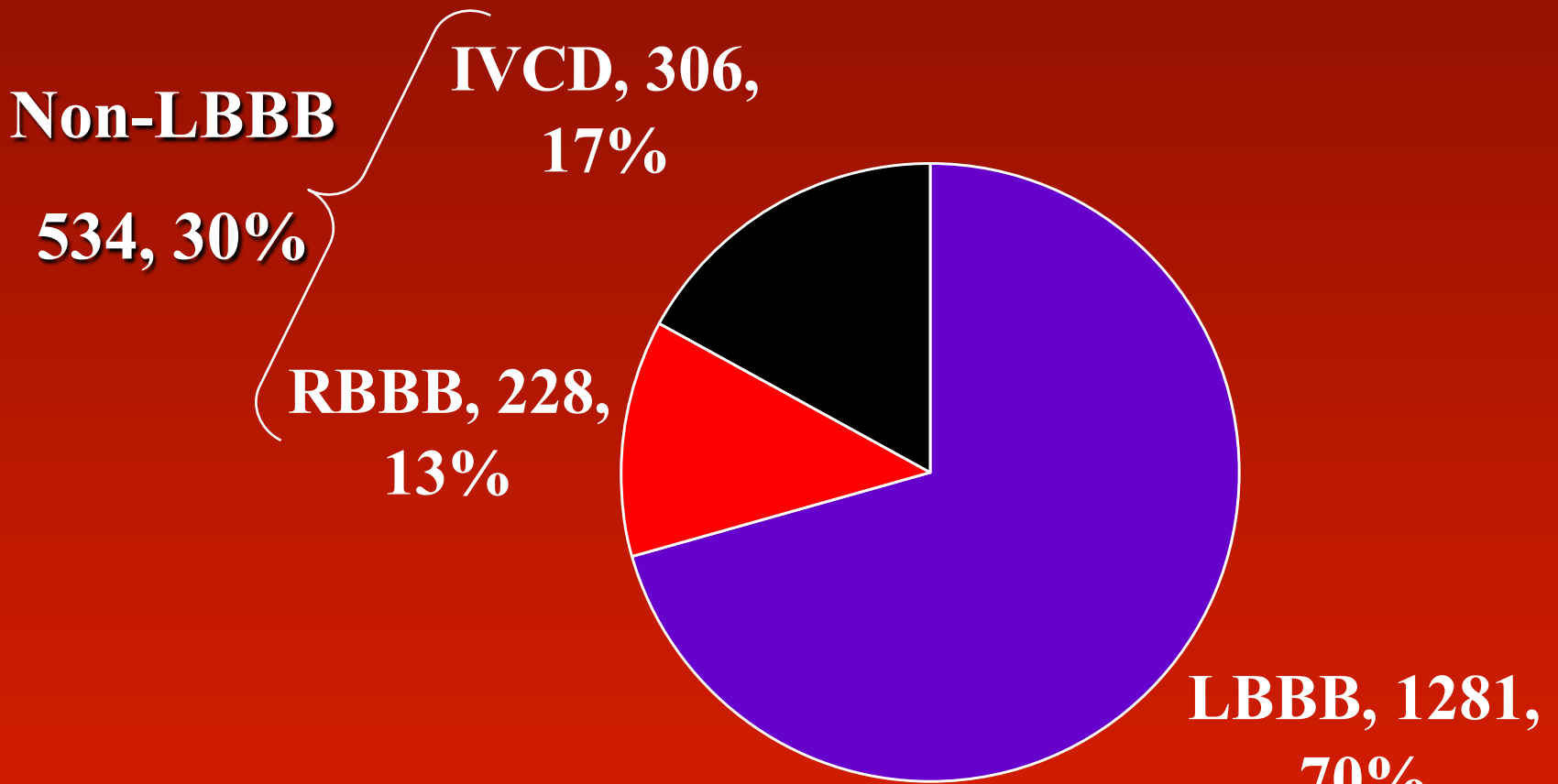
ICD only
N=731

CRT-D
N=1,089



Moss et al. N Engl J Med 2009;361:1329-1338

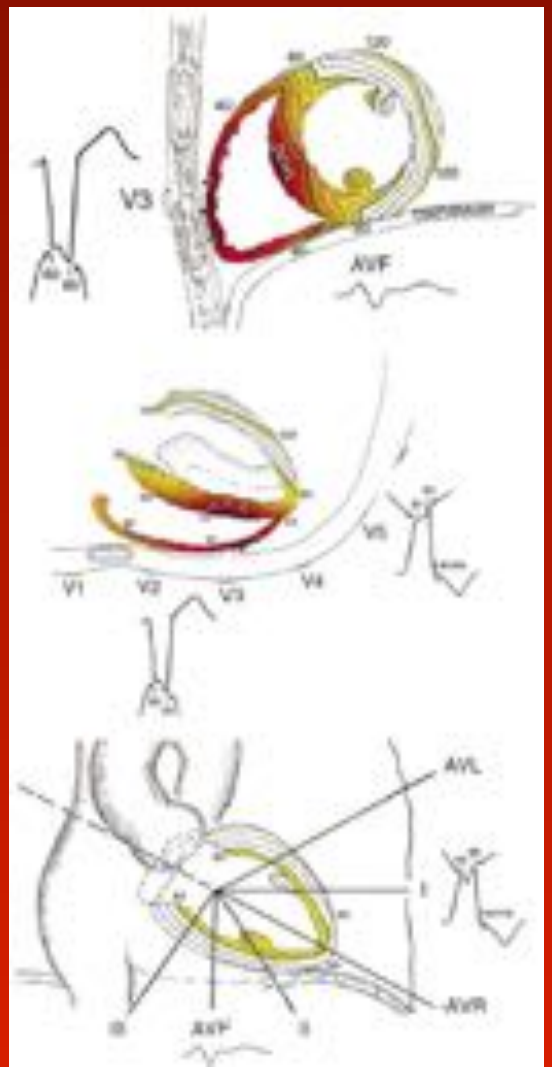
Effects of CRT-D by QRS Morphology in MADIT-CRT



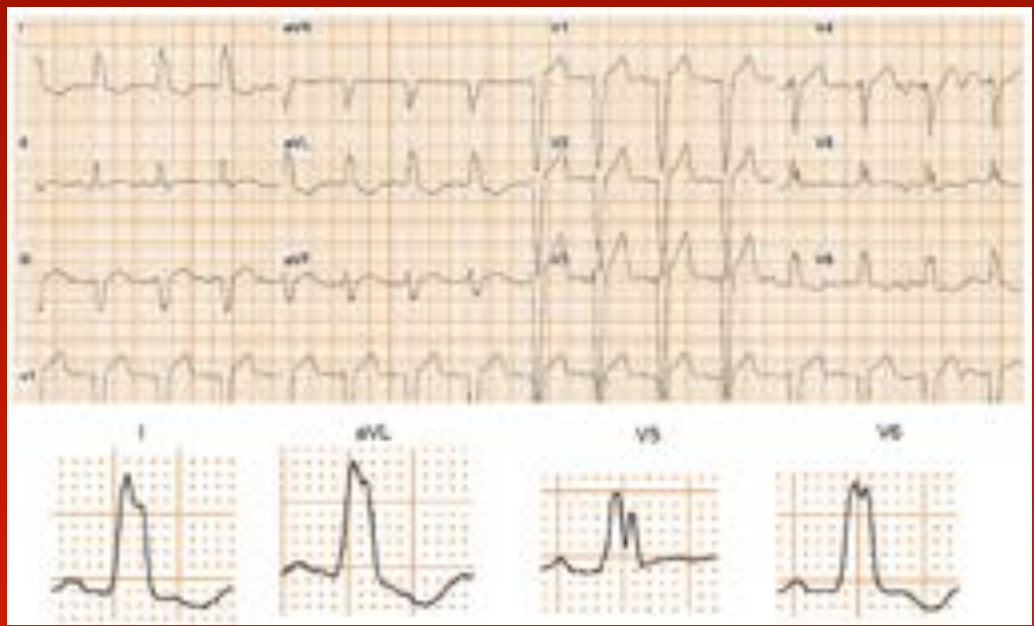
Zareba et al. Circulation 2011;123:1061-1072

Defining Left Bundle Branch Block in the Era of Cardiac Resynchronization Therapy

David G. Strauss, MD, PhD[a,b,*], Ronald H. Selvester, MD[c], and Galen S. Wagner, MD[d]



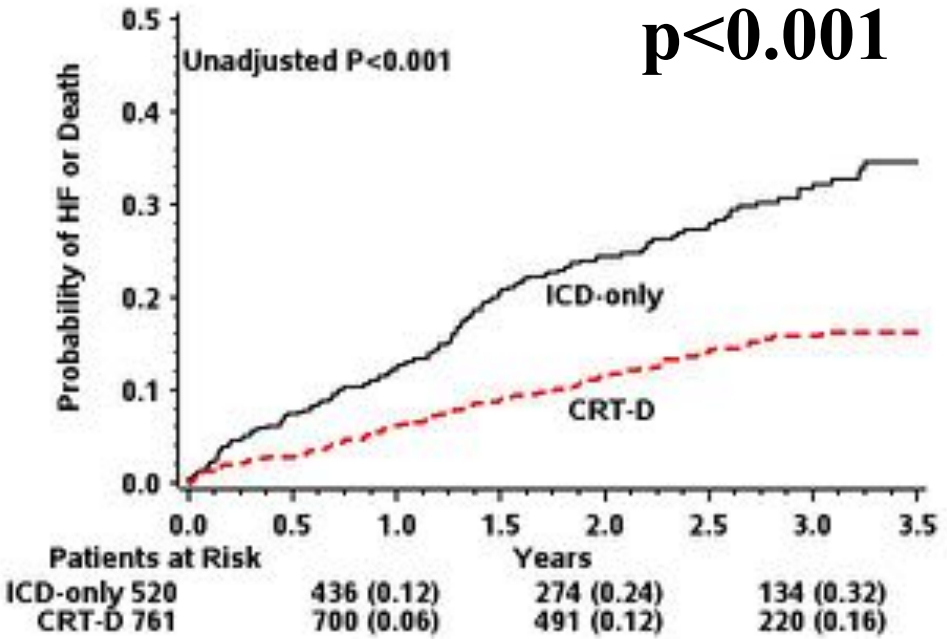
QRS Duration: ≥140 ms for men; ≥130 ms for women along with mid-QRS notching or slurring in >2 contiguous leads: V1, V2, V5, V6, I, and aVL.



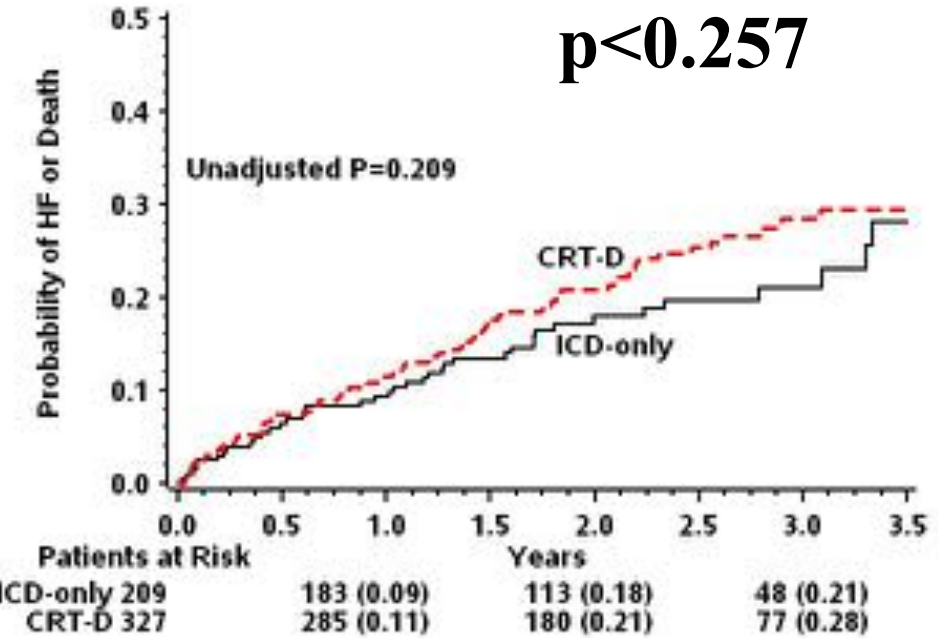
Strauss et al. Am J Cardiol 2011;107:927–934

Cumulative Probability of Heart Failure (HF) Event or Death by Treatment (CRT-D vs. ICD only) in patients with LBBB and Non-LBBB QRS Pattern in MADIT-CRT Patients

HR=0.47
p<0.001



HR=1.24
p<0.257



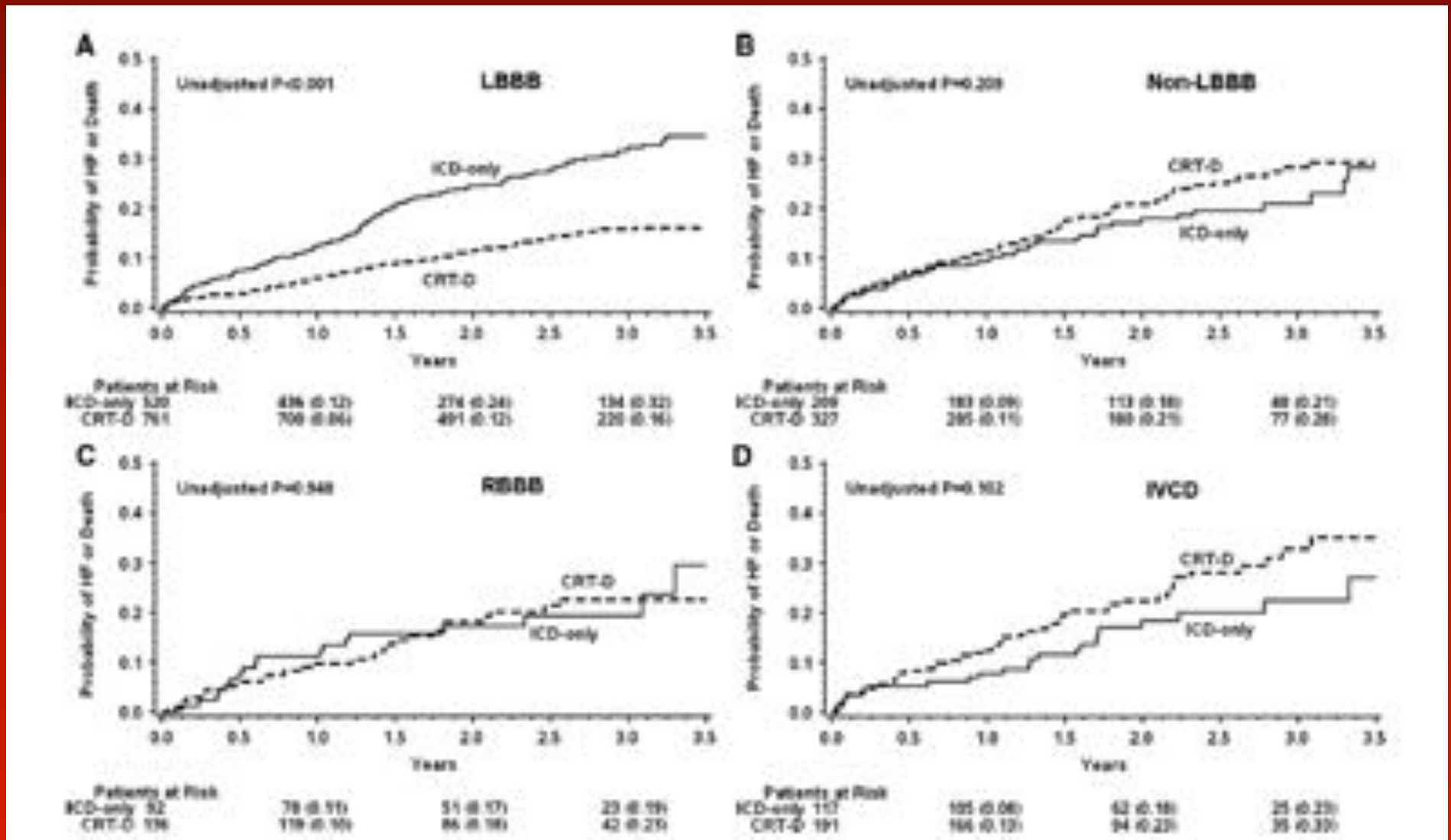
LBBB

Non-LBBB

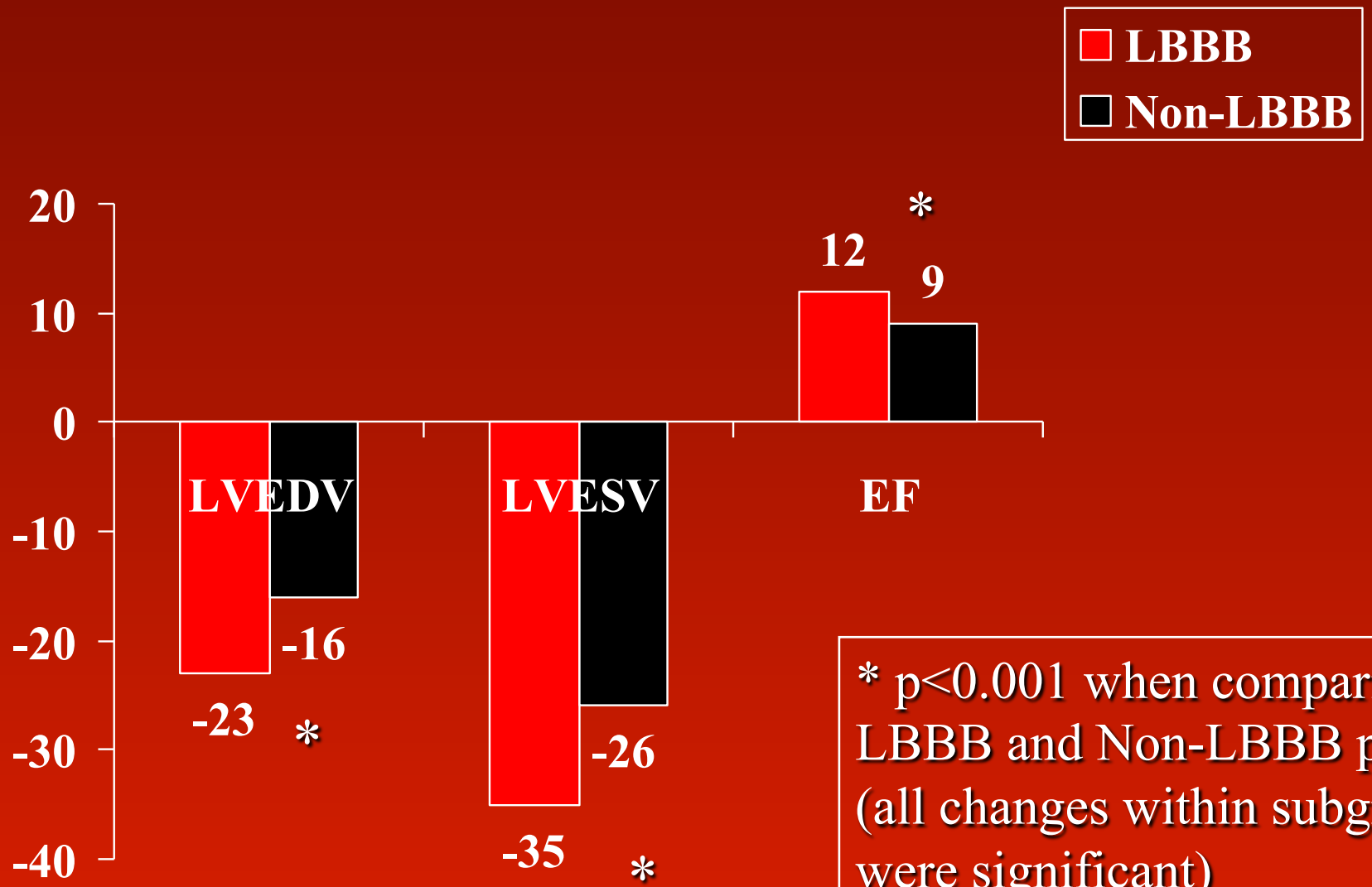
P value for interaction <0.001

Zareba et al. Circulation 2011;123:1061-1072

Probability of HF/Death by QRS Morphology in MADIT-CRT

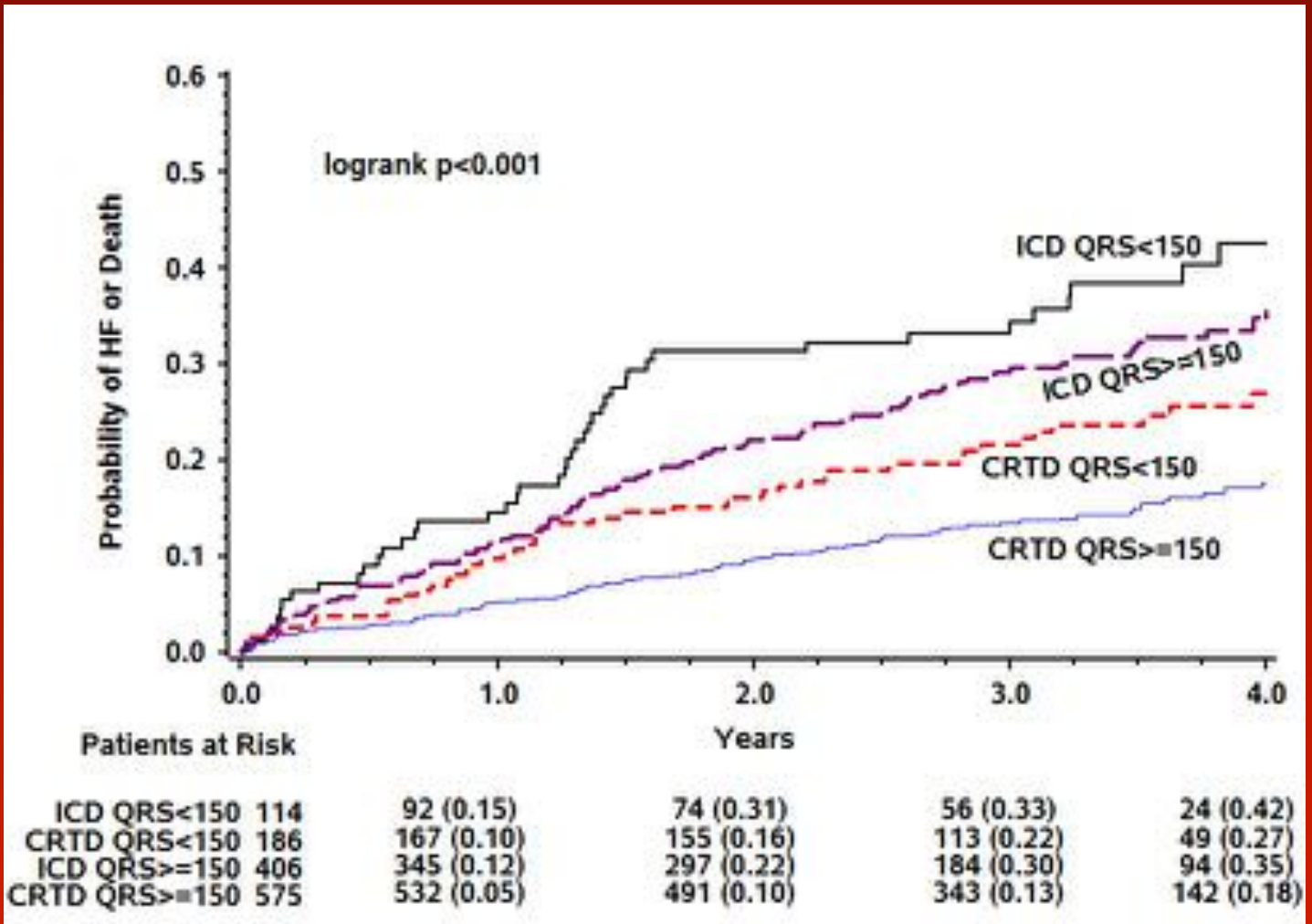


Mean Change in Echocardiographic Parameters from Enrollment to 12 months in CRT-D Patients

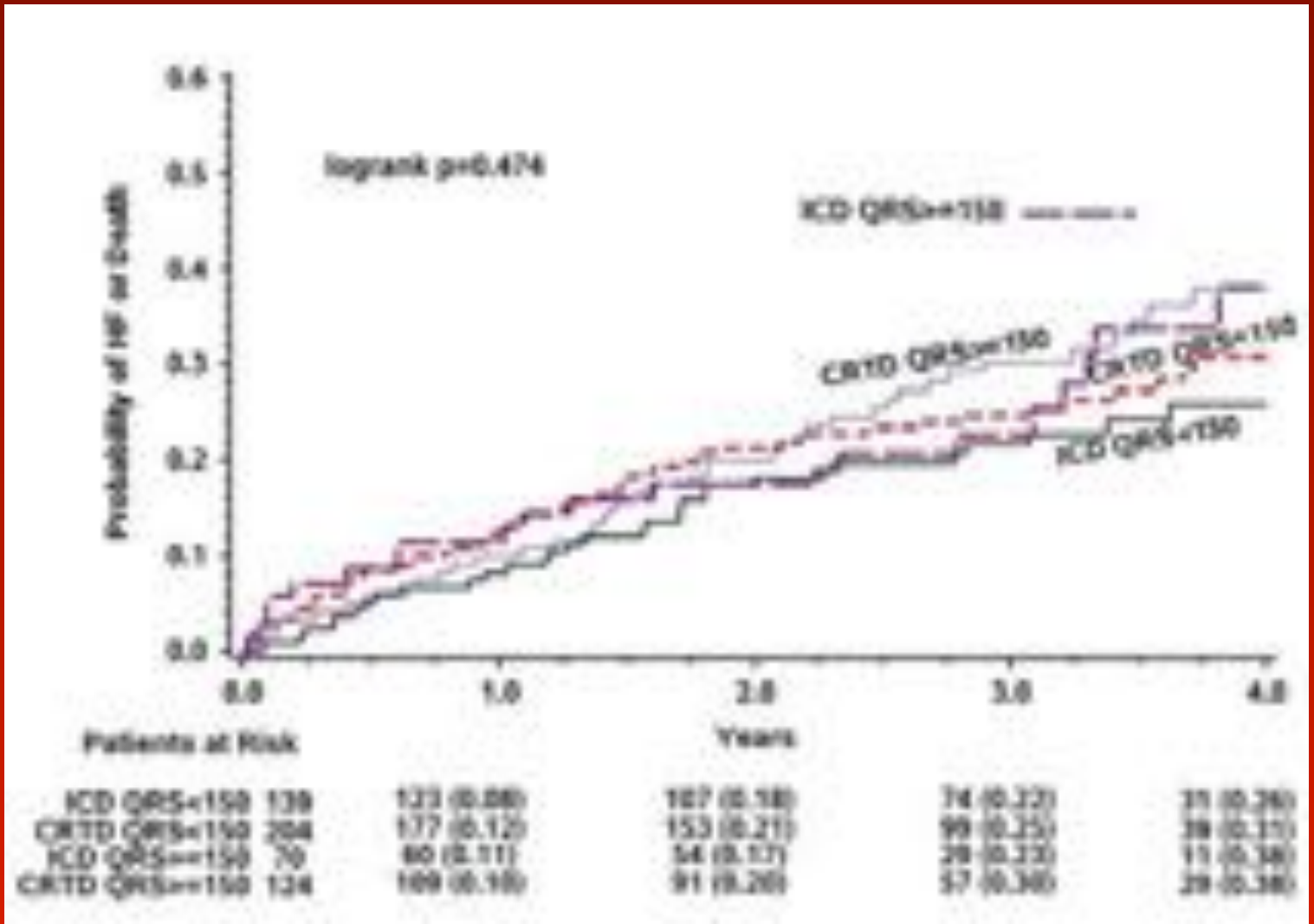


* p<0.001 when comparing LBBB and Non-LBBB patients (all changes within subgroups were significant)

MADIT-CRT: Risks of HF/Death in Subgroups by CRT-D vs. ICD and by QRS duration in LBBB Patients



MADIT-CRT: Risks of HF/Death in Subgroups by CRT-D vs. ICD and by QRS duration in Non-LBBB

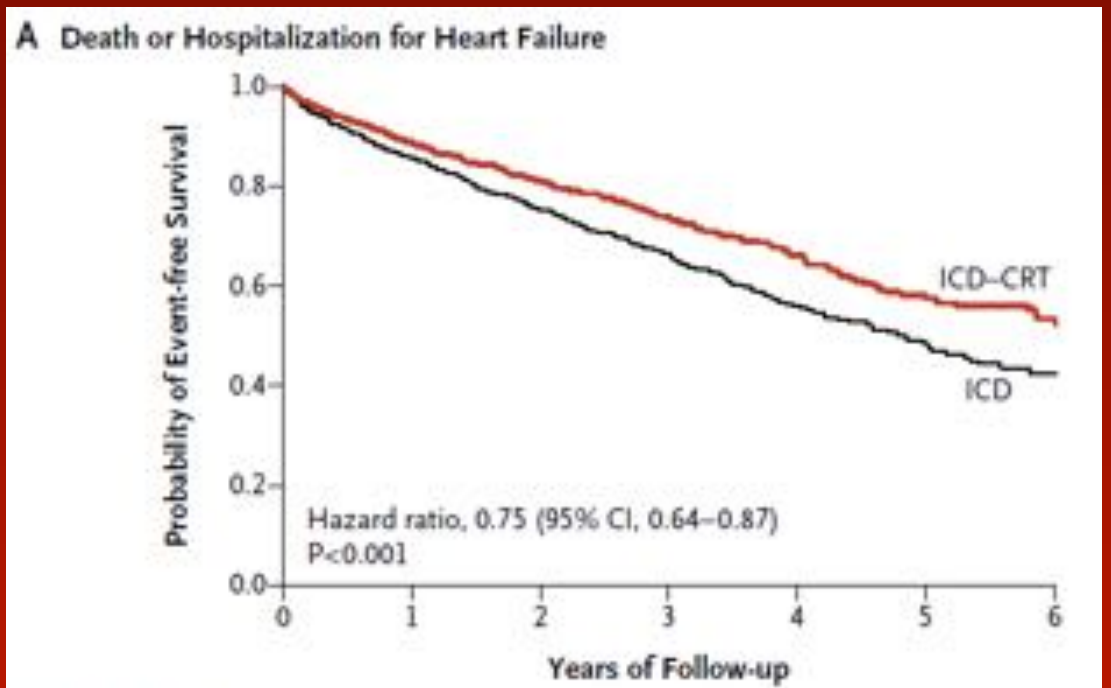


MADIT-CRT: Multivariate Analysis of Risks of HF/Death in Subgroups by CRT-D vs. ICD and by QRS duration

Subgroup	HR	p value	95% CI
LBBB with QRS ≥150 ms	0.45	<0.001	0.34-0.59
LBBB with QRS <150 ms	0.54	0.005	0.35-0.83
			interaction
p=0.464			
Non-LBBB with QRS ≥150 ms	1.00	0.992	0.57-1.75
Non-LBBB with QRS<150 ms	1.04	0.874	0.67-1.61
			interaction
p=0.928			

Multivariate model after adjustment for age≥65, creatinine, current smoking, diabetes, diastolic blood pressure, systolic blood pressure, heart rate, ischemic status,

Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT)



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		

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

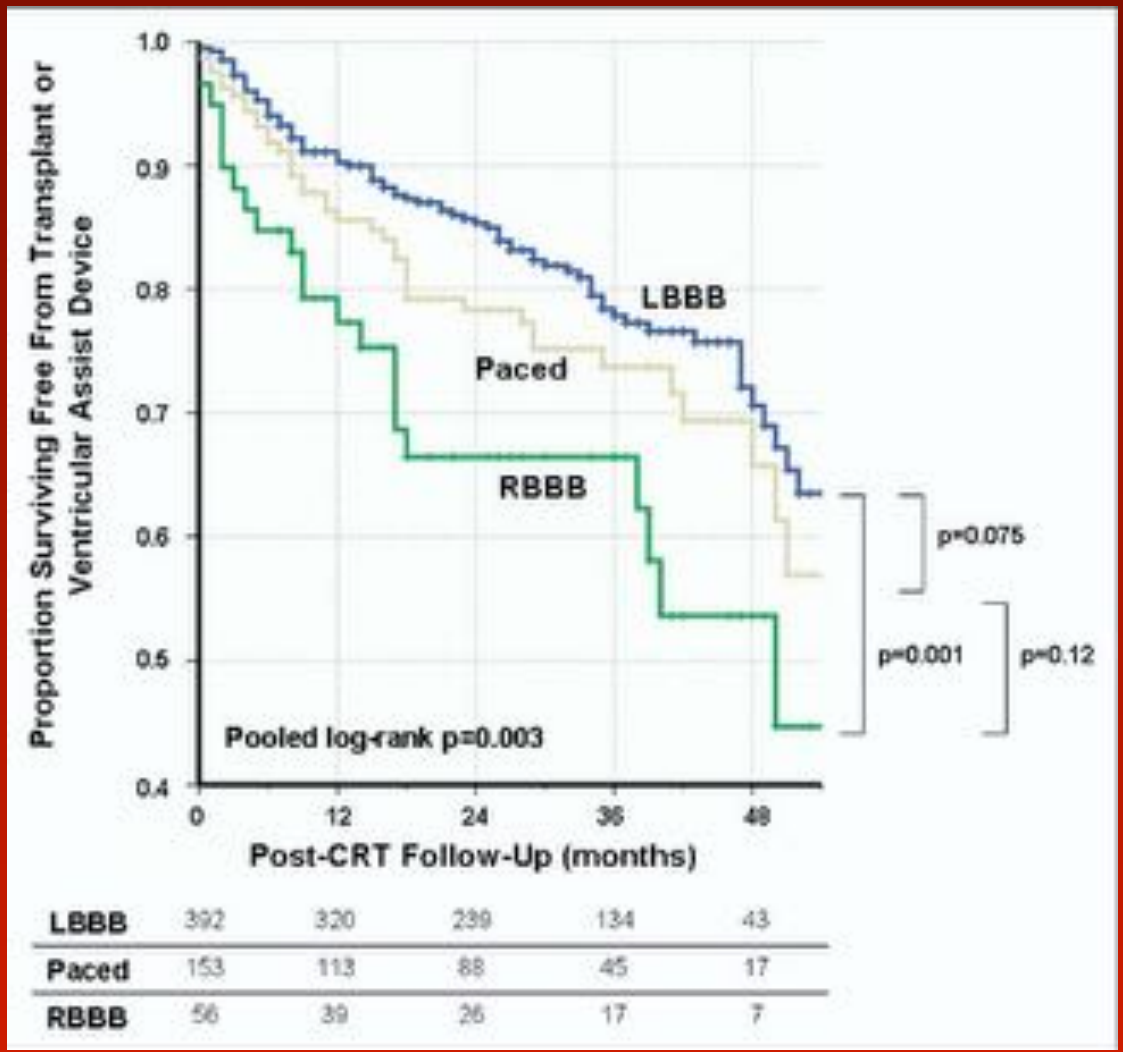
Mortality after CRT by QRS Morphology*

QRS Morphology		HR	95% CI	P value
LBBB	(n=228)	1.0	-	-
RBBB	(n=36)	3.6	(2.0-6.8)	<0.001
IVCD	(n=43)	1.7	(0.9-3.2)	0.091
QRS<120	(n=30)	1.3	(0.6-2.8)	0.520
Paced	(n=167)	1.3	(0.8-2.1)	0.277

* Adjusted for age, sex, ischemic status, NYHA class, creatinine, hemoglobine, lead location

Wokhlu et al. Heart Rhythm 2009;6:1439 –1447

Survival After CRT by QRS Morphology



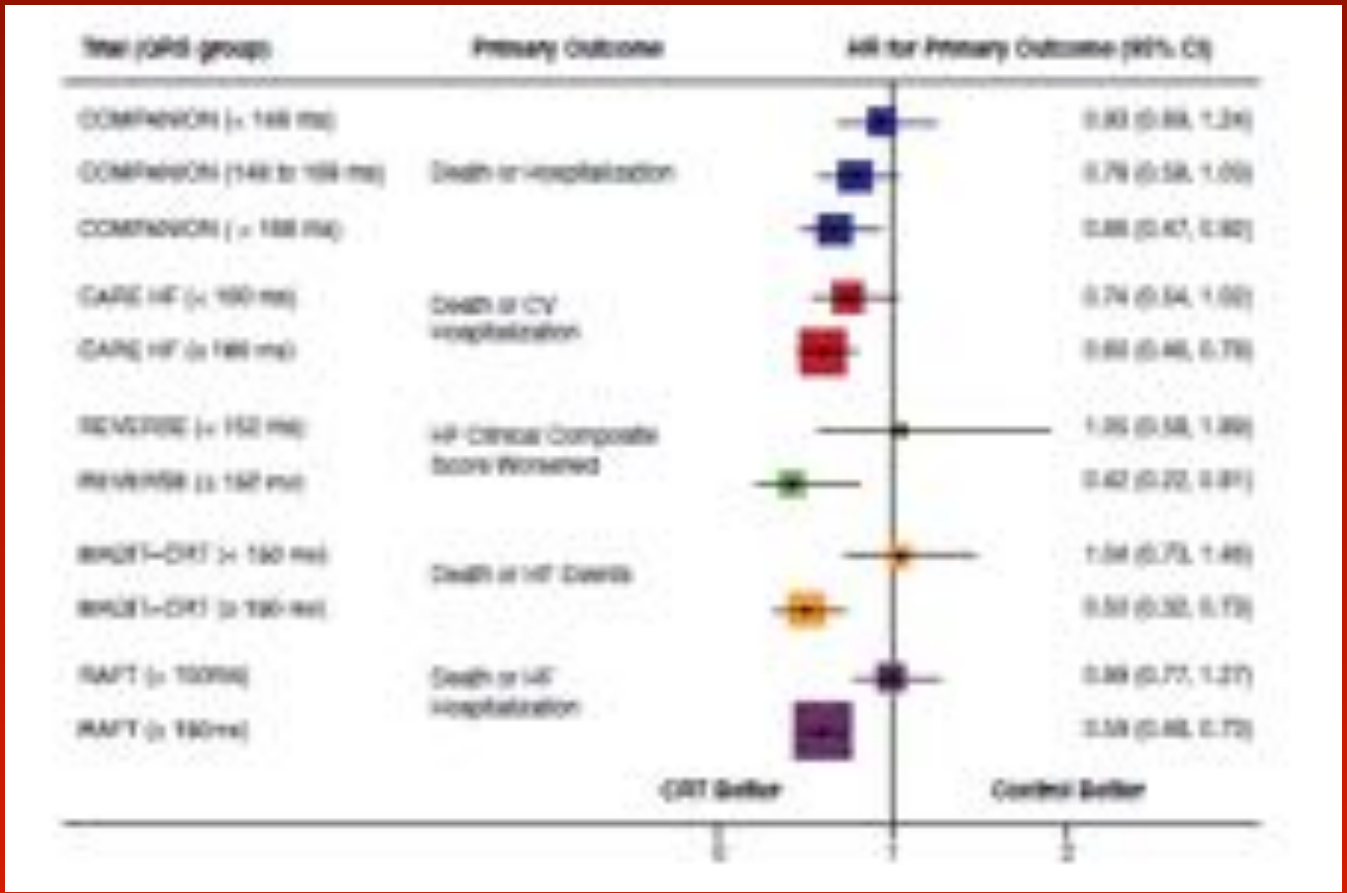
Adelstein and Saba. Am J Cardiol 2009;103:238 –242

Association between QRS duration and outcome with cardiac resynchronization therapy: A systematic review and meta-analysis

Adam R. Bryant, MD,[1] Stephen B. Wilton, MD, MSc,*,[1] Michael P. Lai, Derek V. Exner, MD, MPH

Libin Cardiovascular Institute of Alberta, University of Calgary, Canada

Journal of Electrocardiology 46 (2013) 147–155



Cardiac resynchronization therapy: Forget QRS duration but do not forget QRS morphology

Zareba W J Electrocardiol 2013;46:145-6

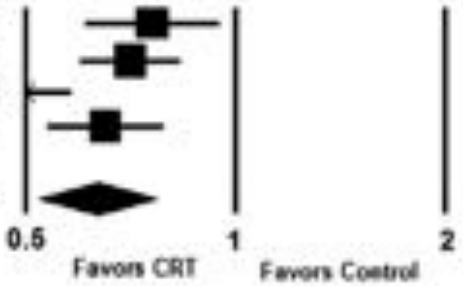
The most recent guidelines (Sept 2012) endorsed a class IIa indication for using CRT in non-LBBB QRS morphology patients. The guidelines suggest "a use of CRT in non-LBBB patients with QRS ≥150 in the NYHA class III or IV based on level of evidence A."

There are no data providing level A evidence indicating that non-LBBB patients with QRS ≥150 benefit from CRT.

Meta-analysis of CRT trials by QRS Morphology

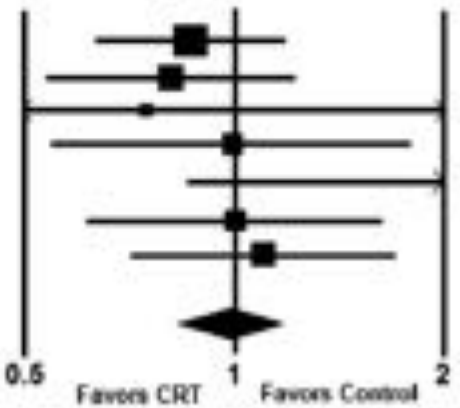
LBBB

Study name	Risk Ratio	Lower Limit	Upper limit	Z-Value	p-Value
COMPANION[10] - LBBB	0.76	0.61	0.95	-2.43	0.016
CARE-HF[11,32] - LBBB	0.70	0.60	0.83	-4.21	<0.0001
MADIT-CRT[12,13,15] - LBBB	0.45	0.35	0.58	-6.20	<0.00001
RAFT[14] - LBBB	0.65	0.54	0.79	-4.44	0.00001
Meta Analysis	**0.64**	**0.52**	**0.77**	**-4.55**	**0.00001**



Non-LBBB

Study name	Risk Ratio	Lower Limit	Upper Limit	Z-Value	p-Value
COMPANION[10] - Non-LBBB	0.86	0.63	1.17	-0.96	0.34
CARE-HF[11,32] - RBBB	0.81	0.54	1.22	-0.99	0.32
CARE-HF[11,32] - IVCD	0.75	0.24	2.33	-0.50	0.62
MADIT-CRT[12,13,15] - RBBB	0.99	0.55	1.79	-0.03	0.97
MADIT-CRT[12,13,15] - IVCD	1.44	0.88	2.36	1.45	0.15
RAFT[14] - RBBB	1.00	0.62	1.62	0.00	1.00
RAFT[14] - IVCD	1.10	0.71	1.69	0.43	0.67
Meta Analysis	**0.97**	**0.82**	**1.15**	**-0.32**	**0.75**



Sipahi et al. Am Heart J 2012;163:260-267.e3

Hazard Ratios for Primary Endpoint by QRS Morphology and Duration by Gender

	Males			Females		
	n	HR	P value	n	HR	P value
QRS Duration						
<140 ms	240	1.69	0.063	61	0.20	0.008
140-159 ms	465	0.77	0.164	178	0.31	0.001
160-179 ms	417	0.51	0.003	153	0.42	0.036
≥180 ms	242	0.50	0.019	61	0.33	0.100
QRS Morphology						
LBBB*	887	0.56	<0.001	394	0.25	<0.001
Non-LBBB	477	1.25	0.273	59	1.55	0.516
RBBB	210	0.94	0.841	18	NA	
IVCD	267	1.49	0.133	41	1.31	0.701

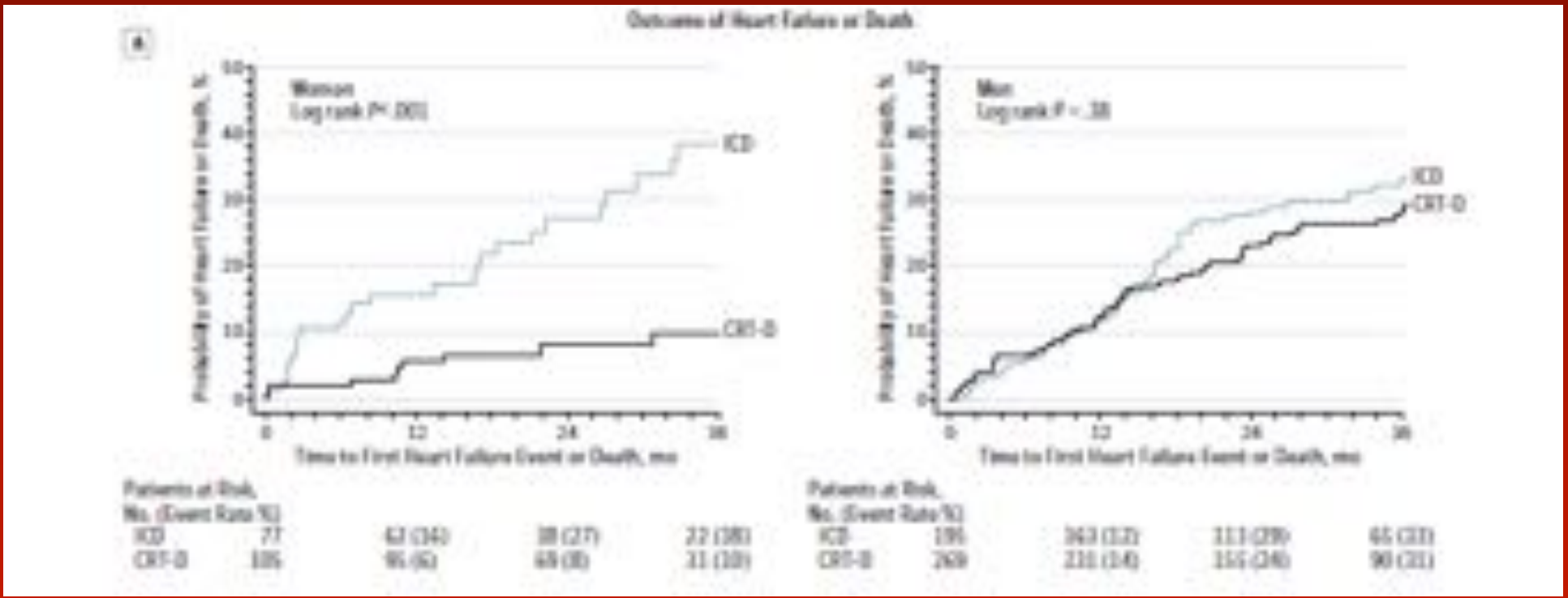
* p=0.006 for interaction comparing HR = 0.56 in males vs. HR = 0.25 in females

Pooled REVERSED, MADIT-CRT, and RAFT Data Analyses by FDA

Trial Characteristic	REVERSE[5]	MADIT-CRT[3]	RAFT[4]
Year	2008	2009	2010
Patients, No.	610	1820	1798
Patients included in meta-analysis, No.	593	1820	1663
Design	CRT on vs CRT off (2:1)[a]	CRT-D vs ICD (3:2)	CRT-D vs ICD (1:1)
Inclusion criteria	NYHA class I/II, LVEF ≤40%, QRS ≥120 ms	NYHA class I/II, LVEF ≤30%, QRS ≥130 ms	NYHA class II/III, LVEF ≤30%, QRS ≥120 ms[b]
Primary end point	HF composite response	Death or HF	Death or HF
Follow-up, median, y	1.1	2.2	4.7
Age, mean, y	63	65	66
Men, %	79	74	83
LVEF, mean, %	27	24	23
Ischemic cardiomyopathy, %	55	55	67
NYHA heart failure class, %	I, 18 II, 82	I, 15 II, 85	II, 80 III, 20
QRS duration, mean, ms	153	158	158
LBBB, %	77	70	66

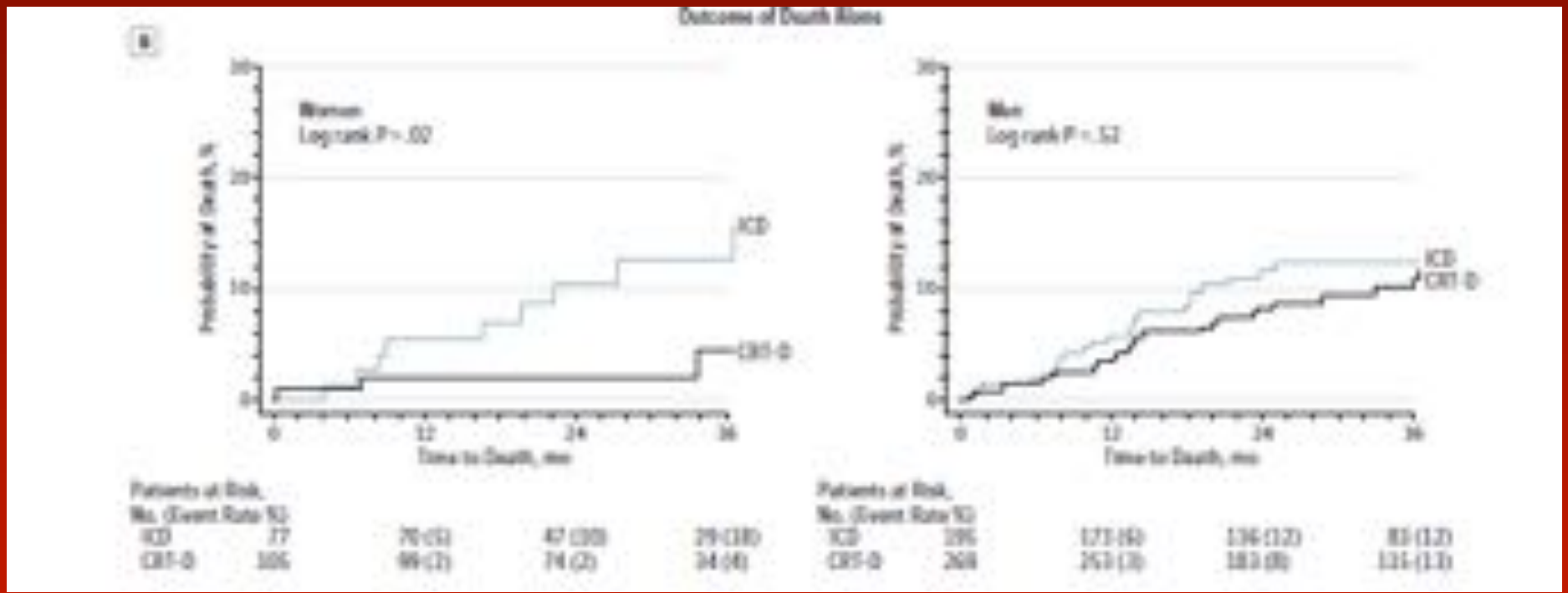
Zusterzeel et al. JAMA 2014

HF or Death in LBBB Patients with QRS of 130-149 ms by Gender



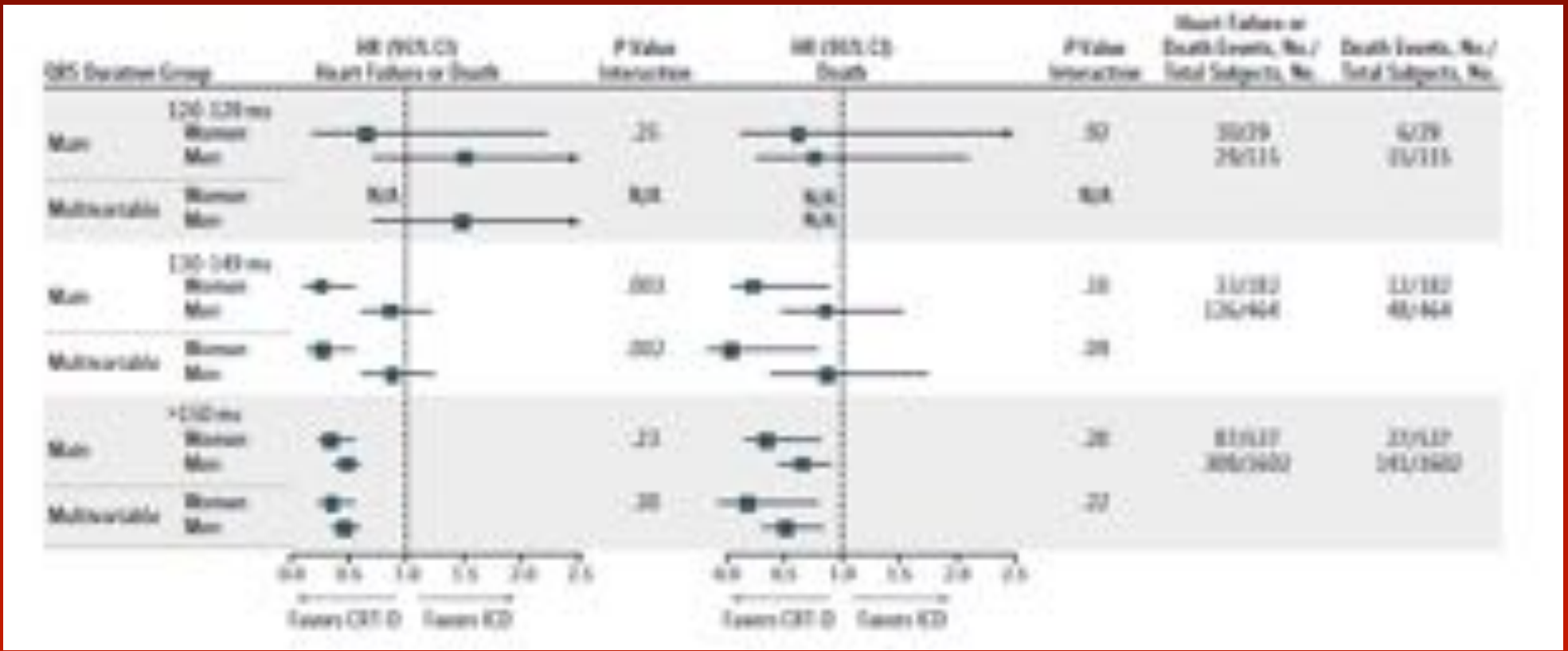
Zusterzeel et al. JAMA 2014

Death in LBBB Patients with QRS of 130-149 ms by Gender



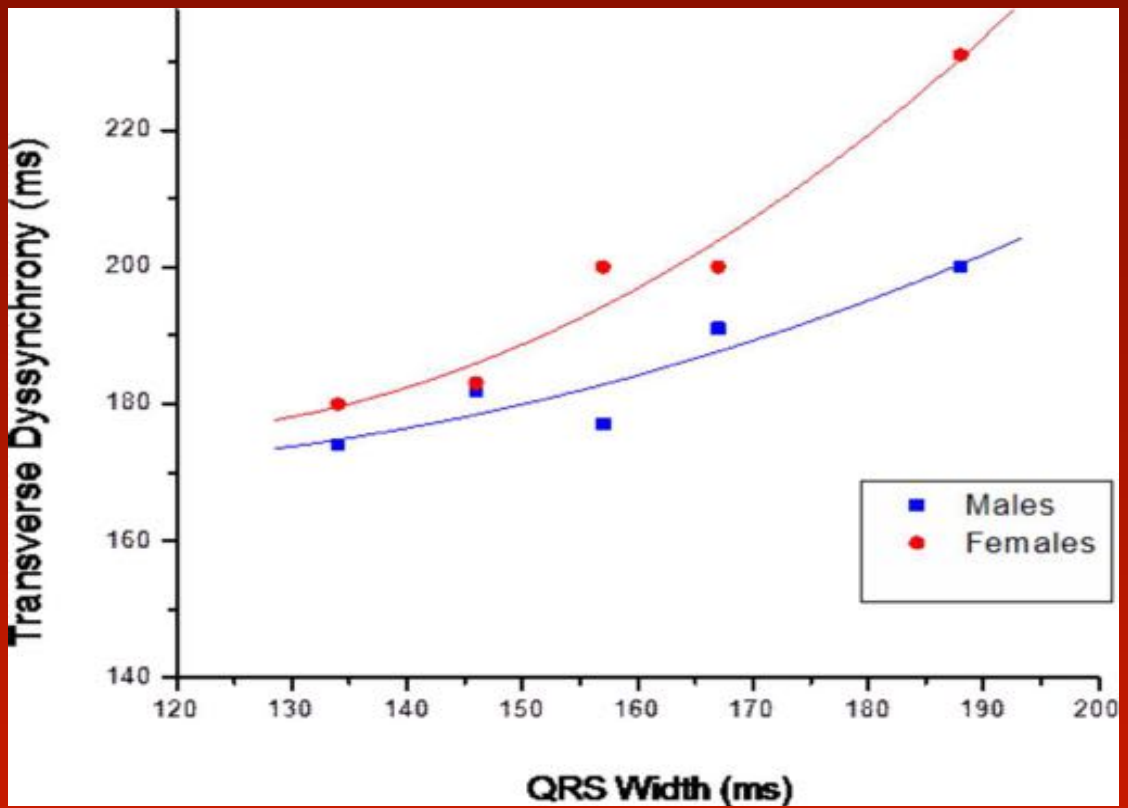
Zusterzeel et al. JAMA 2014

CRT-D vs ICD by QRS Duration and Gender



Zusterzeel et al. JAMA 2014

Mechanical Dyssynchrony in Relationship to QRS by Gender



The relationship between dyssynchrony and QRS duration was shifted by gender.

Women had greater mechanical dyssynchrony for any given QRS width, even after adjusting for QRS morphology, body surface area, EF and disease etiology (p=0.023; graph).

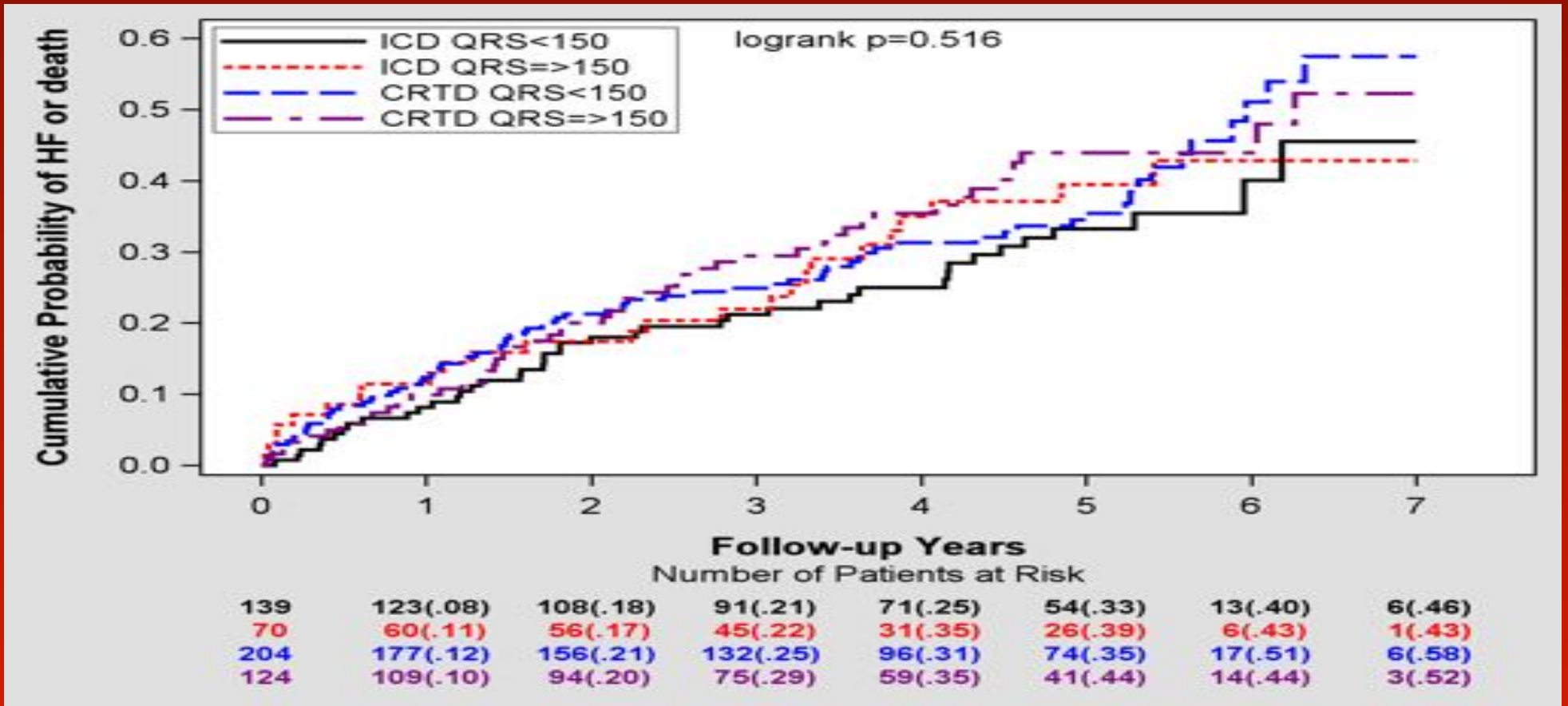
A woman with a QRS of 130 ms had a similar degree of mechanical dyssynchrony as a man with a QRS of 150ms.

Knappe et al. ACC 2011

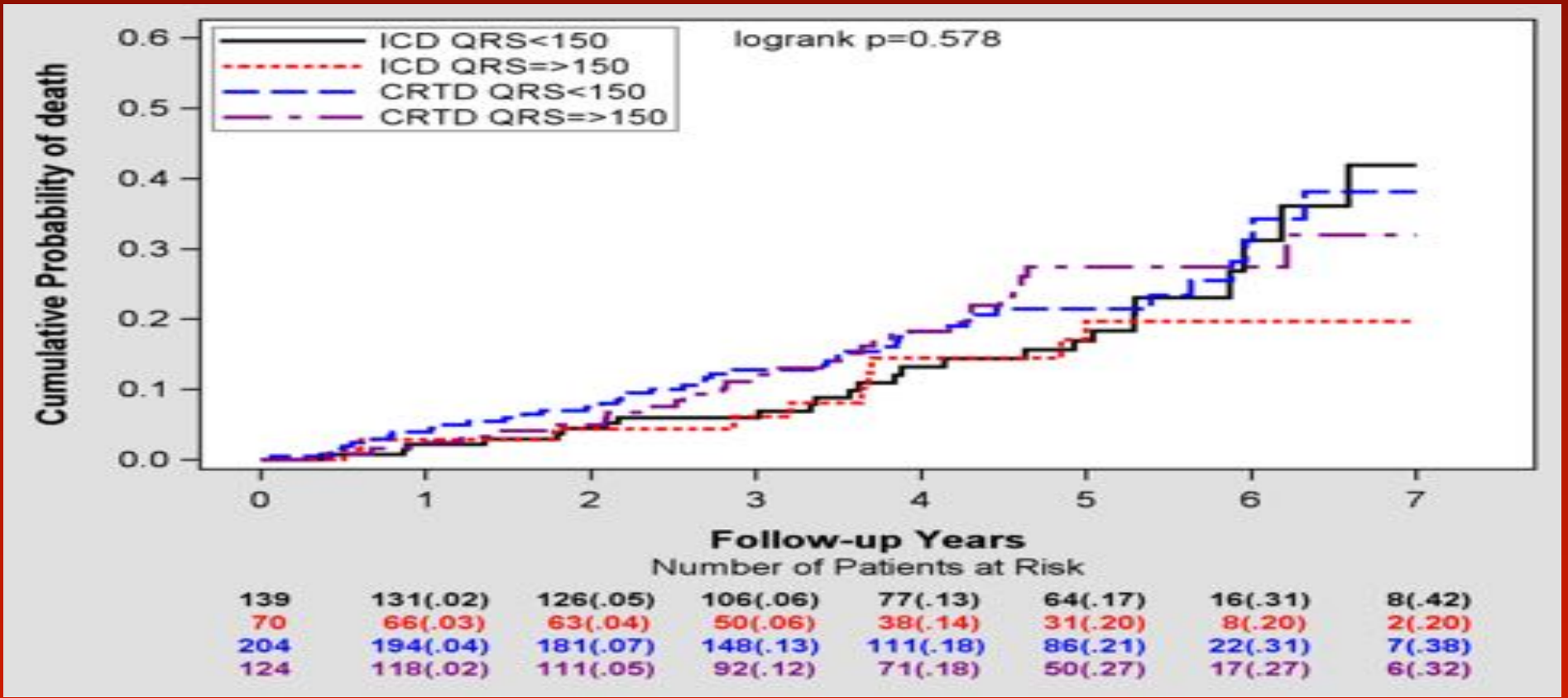
Comparison of Clinical Characteristics in 537 Non-LBBB Patients by QRS Duration in MADIT-CRT

	<150 msec (n=343)	≥150 msec (n=194)
Age at enrollment (mean±SD)	65.0±10.6	64.6±10.1
Female (n, %)	40 (12)	19 (10)
CRT-D Assigned treatment (n, %)	204 (59)	124 (64)
Ischemic (n, %)	277 (81)	158 (81)
RBBB (n, %)	105 (31)	123 (63)*
Creatinine≥1.4 mg/dl (n, %)	79 (23)	52 (27)
Prior CHF Hospitalization (n, %)	111 (33)	78 (41)
Diabetes (n, %)	104 (30)	61 (31)
Hypertension (n, %)	220 (64)	125 (65)
Smoking (n, %)	56 (17)	24 (13)
LVEF (mean±SD)	30±3	30±3
LVEDV Indexed by BSA (mean±SD)	115±20	120±26*

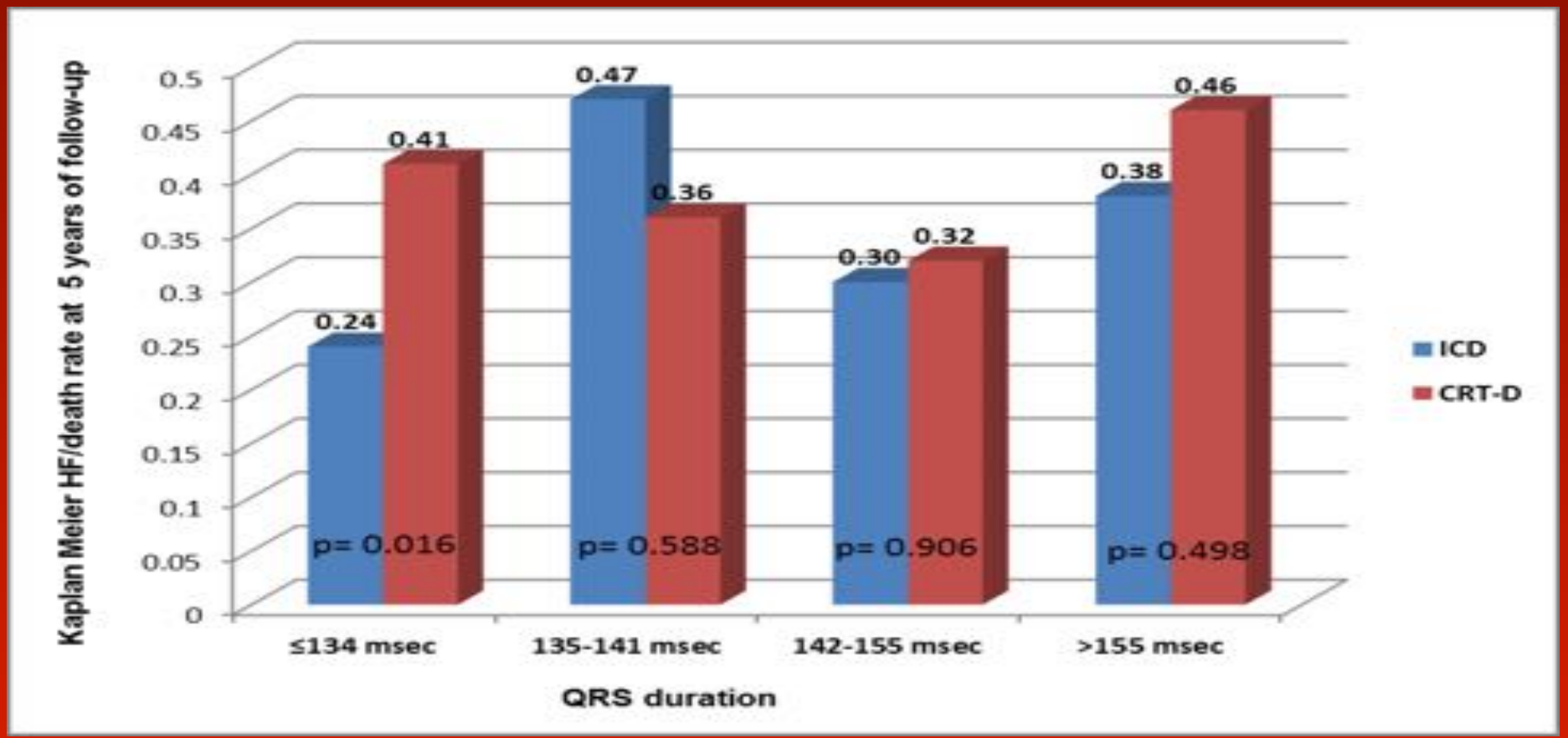
Cumulative Probability of HF/Death by QRS Duration in Non-LBBB Patients from MADIT-CRT



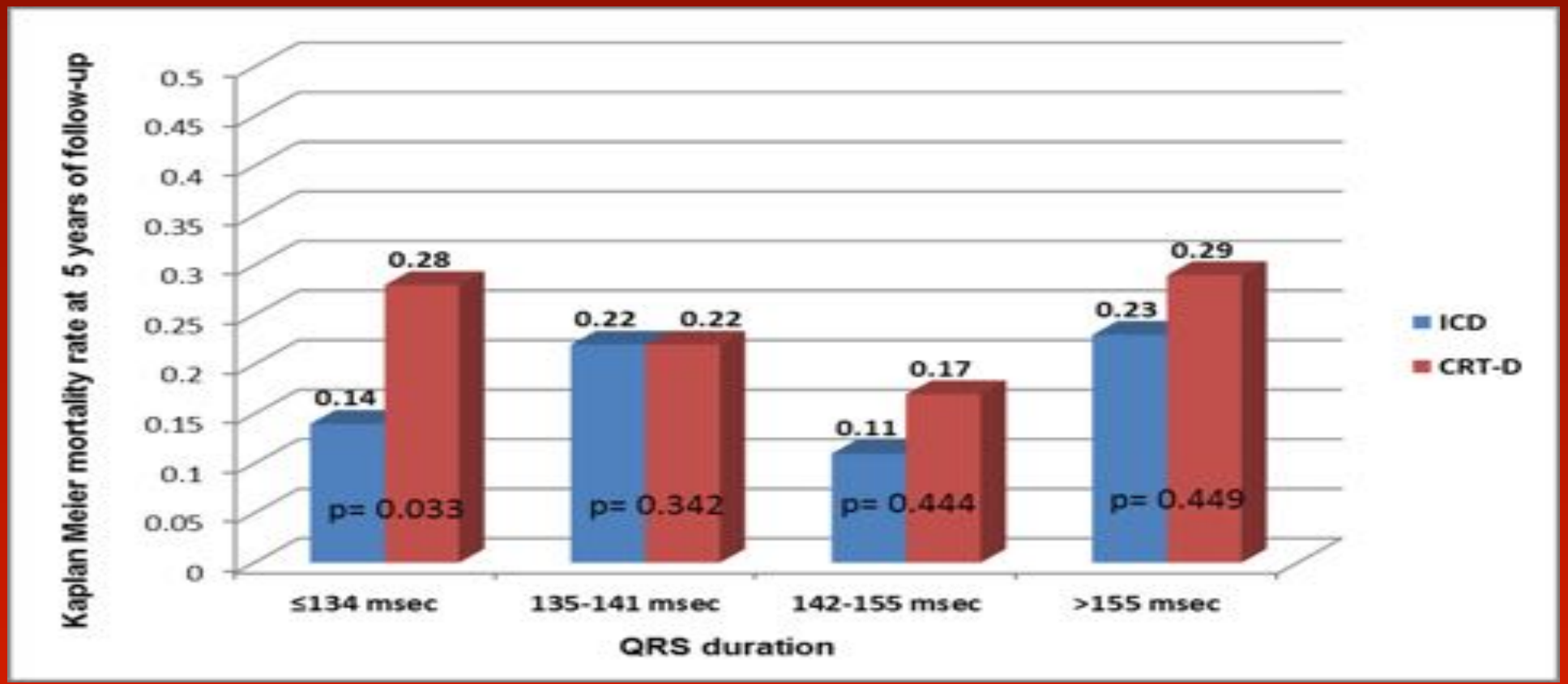
Cumulative Probability of Death by QRS Duration in Non-LBBB Patients from MADIT-CRT



Risk of HF/Death at 5 Years of Follow-up by Treatment Arm and QRS Duration Quartiles in Non-LBBB Patients from MADIT-CRT



Risk of Death at 5 Years of Follow-up by Treatment Arm and QRS Duration Quartiles in Non-LBBB Patients from MADIT-CRT



Risk of Outcome in CRT-D vs ICD-Only Therapy by QRS Duration in Non-LBBB Patients from MADIT-CRT.

Endpoint	HR*	CI	P	P for interaction
Death (n=105)				
Continuous QRS	1.01	0.98-1.04	0.716	
QRS<150 msec	1.26	0.76-2.08	0.370	0.829‖
QRS≥150 msec	1.39	0.67-2.88	0.378	
Q1 (≤134 msec)	2.32	0.97-5.57	0.059	0.121†
Q2-4 (>134msec)	1.06	0.66-1.69	0.812	
Heart Failure or Death (n=187)				
Continuous QRS	1.00	0.98-1.02	0.960	
QRS<150 msec	1.28	0.88-1.87	0.214	0.479‖
QRS≥150 msec	1.02	0.62-1.67	0.943	
Q1 (≤134 msec)	2.37	1.18-4.74	0.015	0.024†
Q2-4 (>134msec)	0.97	0.69-1.36	0.857	

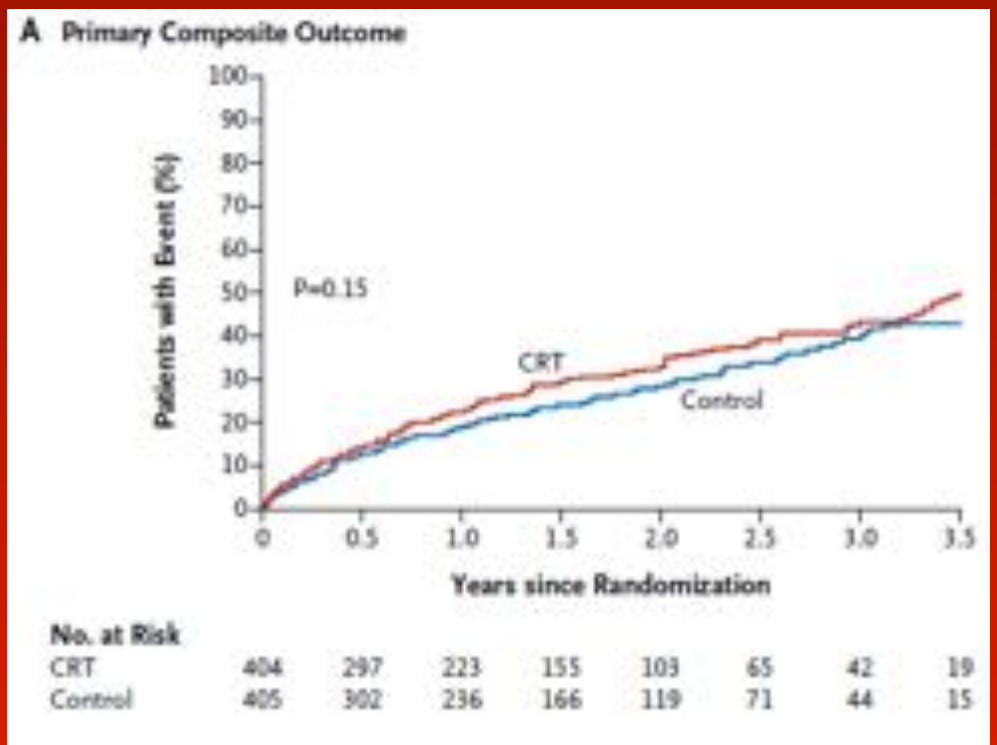
* The model is adjusted for CRTD therapy, Age≥65, Diabetes, DBP>80 mmHg, Creatinine≥1.4mg/dl, Prior HF hospitalization and treatment-by-QRS duration interaction.

‖ QRS <150 msec or ≥150 msec by treatment interaction. † QRS quartiles by treatment interaction.

Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex

Frank Ruschitzka, M.D., William T. Abraham, M.D., Jagmeet P. Singh, M.D., Ph.D., Jeroen J. Bax, M.D., Ph.D., Jeffrey S. Borer, M.D., Josep Brugada, M.D., Ph.D., Kenneth Dickstein, M.D., Ph.D., Ian Ford, M.D., Ph.D., John Gorcsan III, M.D., Daniel Gras, M.D., Henry Krum, M.B., B.S., Ph.D., Peter Sogaard, M.D., D.M.Sc., and Johannes Holzmeister, M.D., for the EchoCRT Study Group*

NEJM 2013



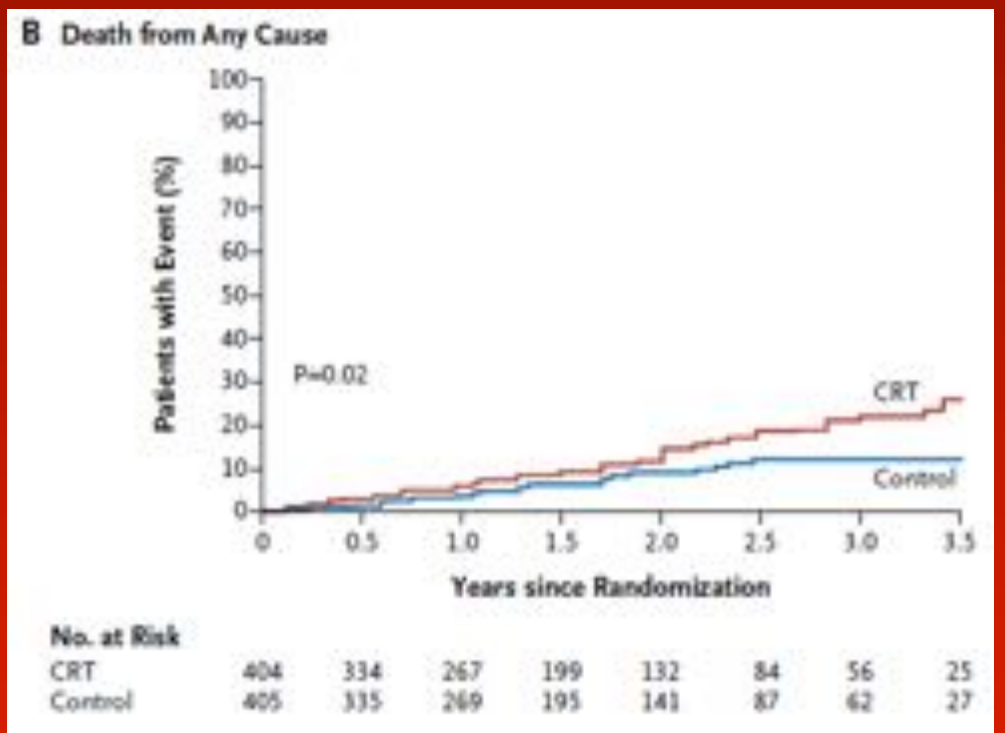
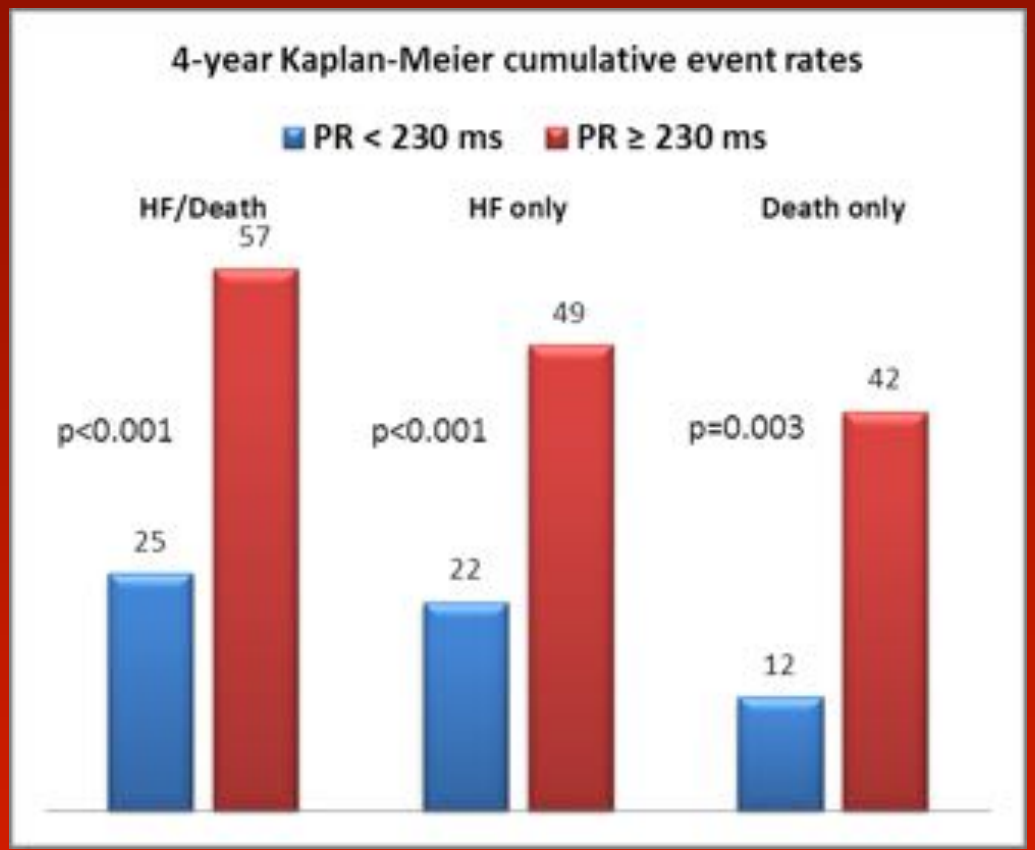


Table 2. **Protocol-Specified Cardiovascular Outcomes.***

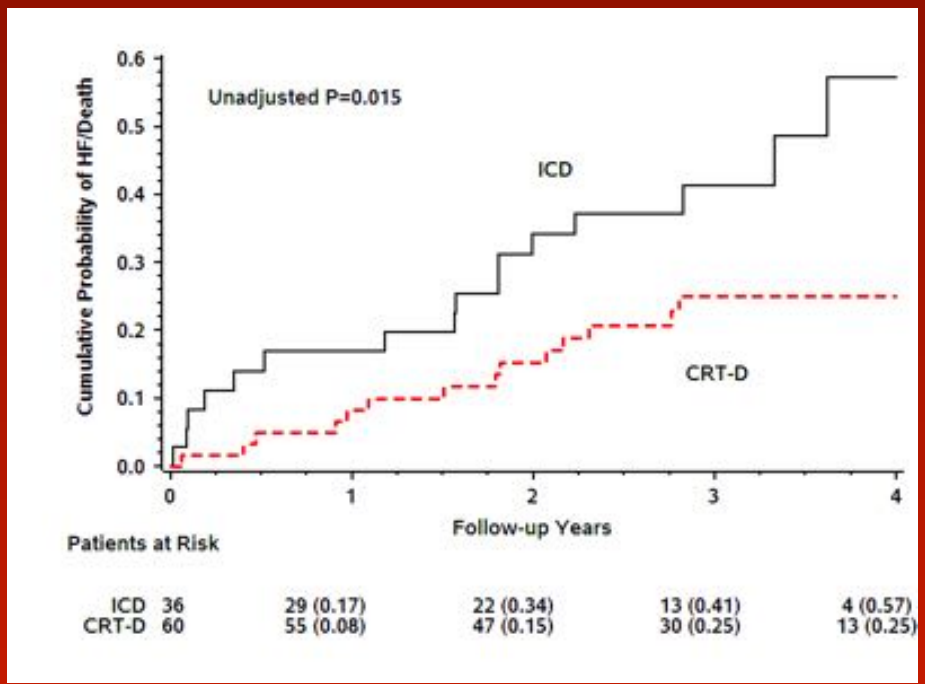
Outcome	Control Group (N = 405)	CRT Group (N = 404)	Adjusted Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite outcome				
Death from any cause or hospitalization for heart failure	102 (25.2)	116 (28.7)	1.20 (0.92–1.57)	0.15
Components of primary outcome				
Hospitalization for heart failure	90 (22.2)	99 (24.5)	1.16 (0.87–1.55)	0.25
Death from any cause	26 (6.4)	45 (11.1)	1.81 (1.11–2.93)	0.02
Other cardiovascular outcomes				
Hospitalization for cardiovascular event	137 (33.8)	147 (36.4)	1.11 (0.88–1.40)	0.36
Death				
Cardiovascular event	17 (4.2)	37 (9.2)	2.26 (1.27–4.01)	0.004
Heart failure	10 (2.5)	17 (4.2)	1.74 (0.80–3.81)	0.15
Follow-up data censored				
Owing to LVAD implantation	10 (2.5)	7 (1.7)	—	—
Owing to heart transplantation	5 (1.2)	3 (0.7)	—	—
Death after data were censored owing to LVAD implantation or heart transplantation†	4 (1.0)	1 (0.2)	—	—

Four-Year Kaplan–Meier Cumulative Probability of HF/Death, HF only, and All-Cause Mortality in ICD Patients with non-LBBB, by baseline PR-interval

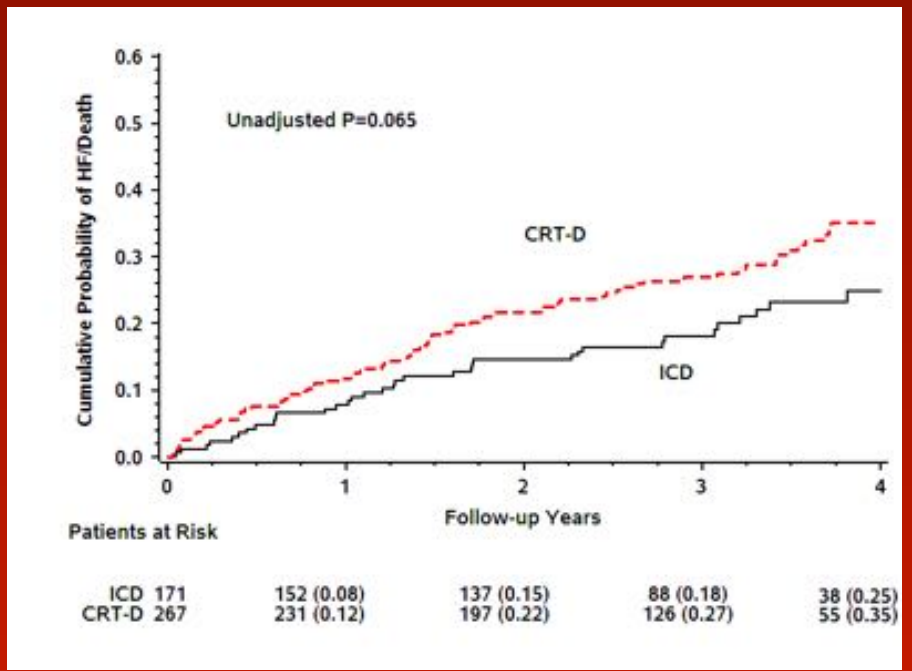


Kutyifa et al. Circ AE

Probability of HF/Death Episodes in Patients with PR ≥ 230 ms and <230 ms



PR≥230



PR<230

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CRT-D vs. ICD therapy on HF/Death, HF only, and All-Cause Mortality in non-LBBB patients by baseline PR-interval

End point	Hazard ratio	95% confidence interval	p-value	Interaction p-value
Heart Failure or Death (141 events/ 478 patients)				
CRT-D: ICD in PR< 230 ms	1.45	0.96-2.19	0.078	<0.001
CRT-D: ICD in PR ≥ 230 ms	0.27	0.13-0.57	<0.001	
All-Cause Mortality (67 events/ 478 patients)				
CRT-D: ICD in PR< 230 ms	2.14	1.12-4.09	0.022	<0.001
CRT-D: ICD in PR ≥ 230 ms	0.19	0.06-0.63	<0.001	

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Conclusions

1. Heart failure patients with mild to moderate heart failure with EF≤30% who present with LBBB derive substantial benefit from CRT-D: reduction in heart failure progression and reduction in the risk of ventricular tachyarrhythmias.
2. No evidence of CRT-D benefit is observed in patients with Non-LBBB QRS pattern regardless of QRS duration.
3. Non-LBBB patients with QRS duration of 130-134 msec are at higher risk for mortality or HF outcome with CRT-D therapy as compared with ICD therapy (similar trend for mortality).
4. Non-LBBB patients with PR≥230 msec show significant redution in cardiac events regardless of QRS duration.