BENEFIT OF CRT IN MILDLY SYMPTOMATIC HEART FAILURE RECENT DATA FROM MADIT-CRT AND RAFT

Ilan Goldenberg MD
Professor of Cardiology
Sheba Medical Center and Tel Aviv University, Israel
University of Rochester Medical Center,
Rochester NY, USA

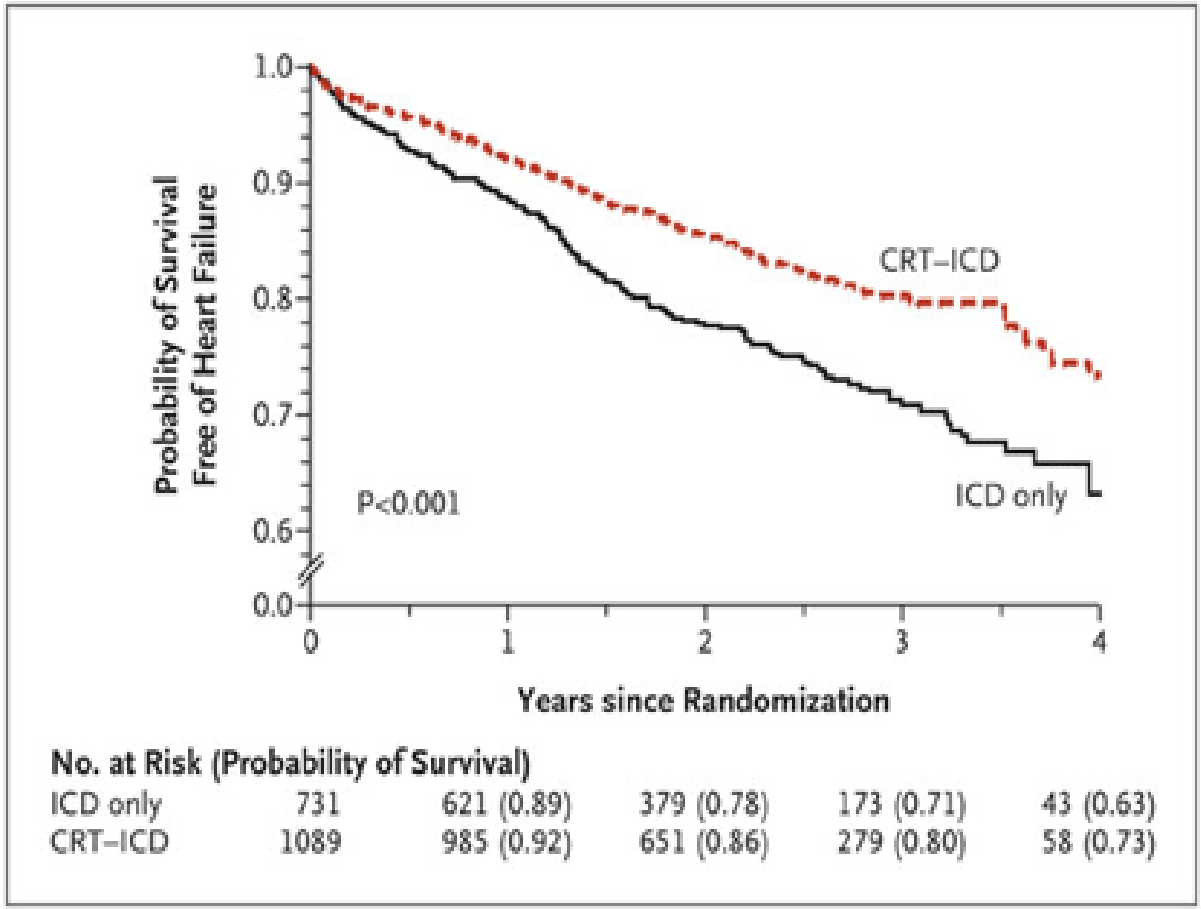
POINTS FOR DISCUSSION

- Reverse remodeling and subsequent outcomes
- Effect in subgroups
- Effect on ventricular and atrial tachyarrhythmias

REVERSE REMODELING AND DYSSYNCHRONY

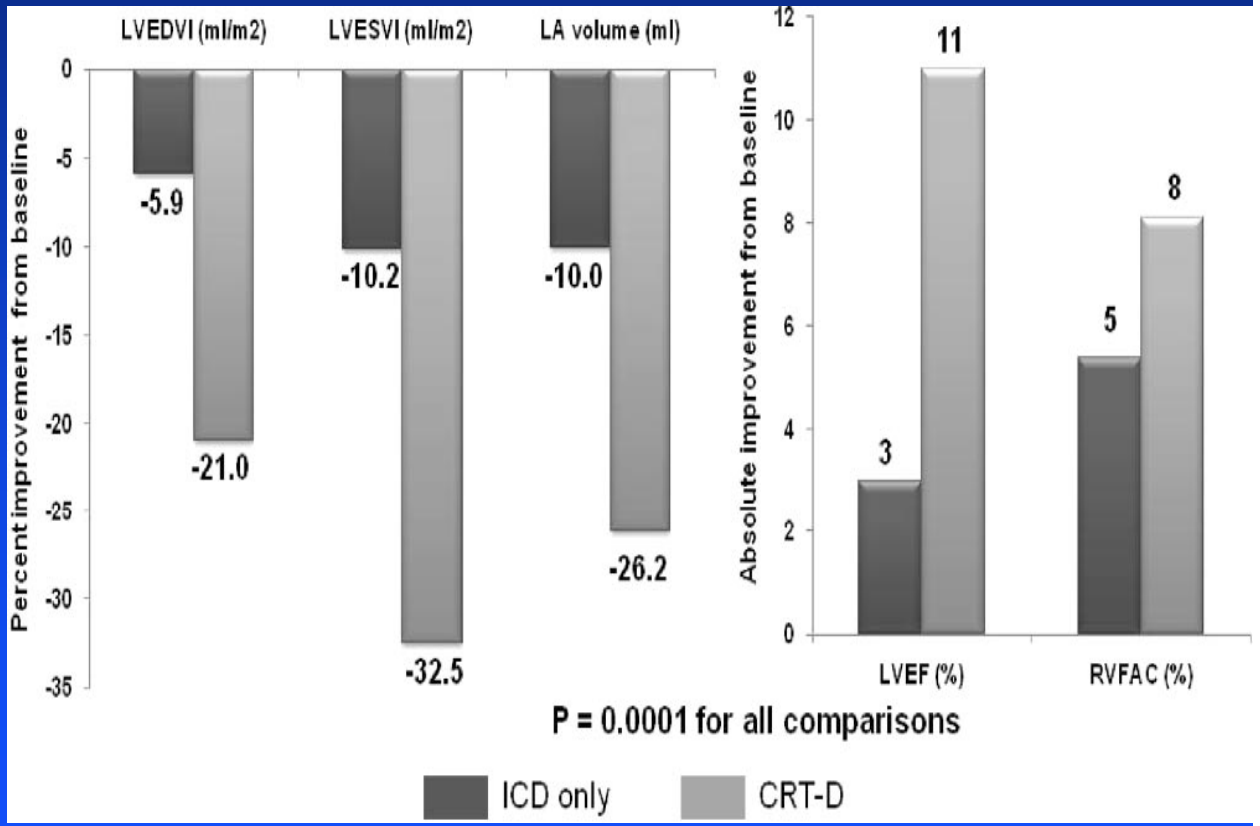
BACKGROUND: MADIT-CRT
Moss et al. NEJM, 2009

- **1820 ICM/NICM pts:**
  - EF ≤ 30%
  - QRS ≥ 130 msec
  - NYHA I/II
- **Randomization:**
  - ↗ CRT-D vs. ICD-only
  - ↗ 3:2 ratio
- **Outcome:**
  - HR=0.66 (p=0.001)



MADIT-CRT: ECHO RESPONSE
Solomon et al et al. Circulation, 2010

- **Improvement at 1 yr:**
  - ↗ LVEDV
  - ↗ LVESV
  - ↗ LAV
  - ↗ LVEF



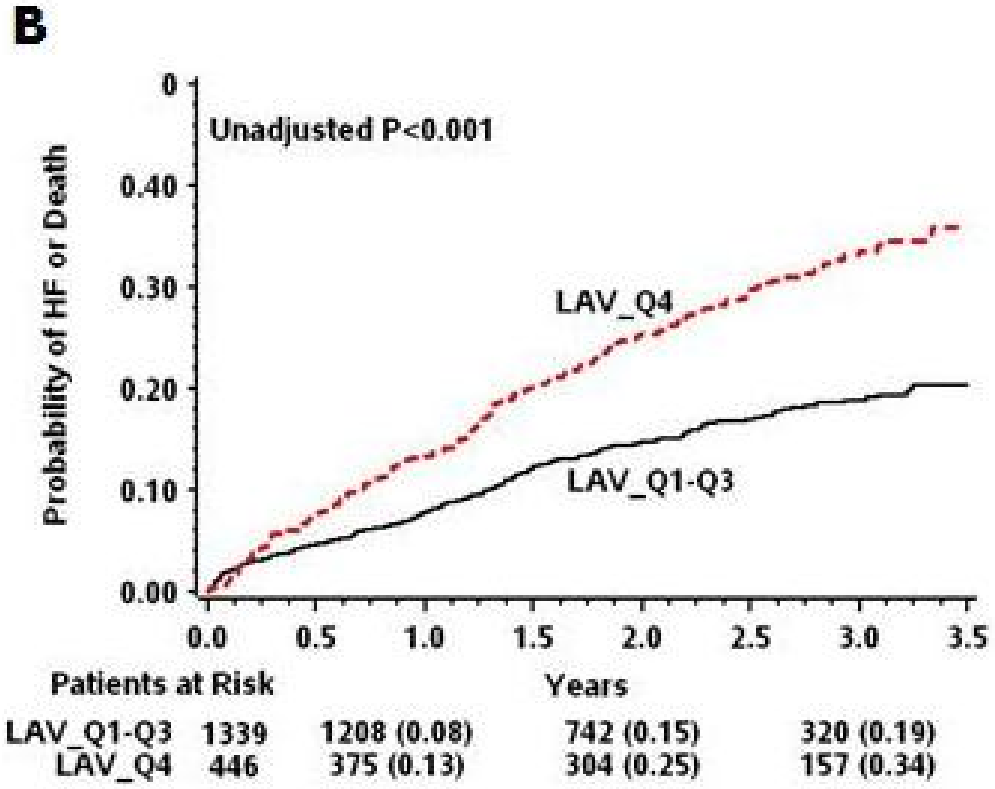
MADIT-CRT: ECHO RESPONSE AND SUBSEQUNT CLINICAL RESPONSE

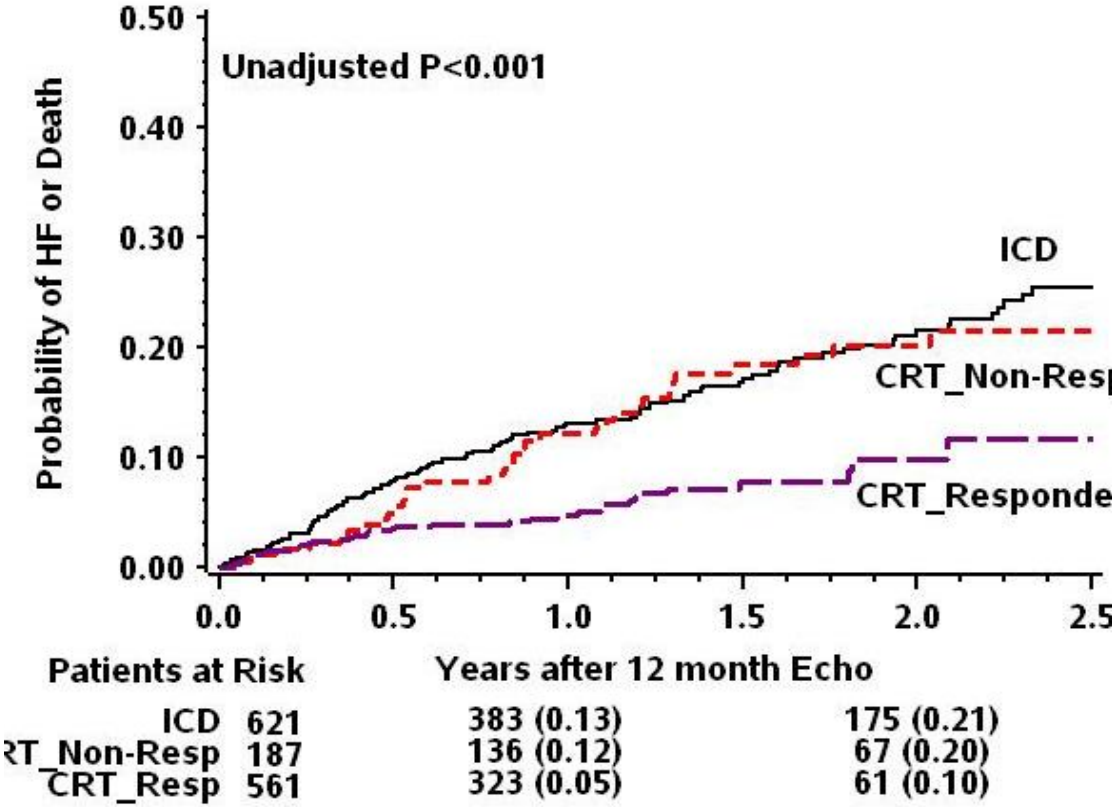
Solomon et al et al. Circulation, 2010

	Primary End Point of First Occurrence of Heart Failure or Death		All-Cause Mortality	
	Adjusted for Treatment and Ischemic Status	Multivariable Adjusted*	Adjusted for Treatment and Ischemic Status	Multivariable Adjusted*
Percent improvement in end-diastolic volume (per 10% decrease)	0.61 (0.51, 0.71)	0.60 (0.51, 0.72)	0.73 (0.54, 0.97)	0.79 (0.59, 1.06)
P	<0.001	<0.001	0.032	0.11
Percent improvement in end-systolic volume (per 10% decrease)	0.72 (0.65, 0.80)	0.72 (0.65, 0.84)	0.79 (0.66, 0.95)	0.83 (0.68, 0.99)
P	<0.001	<0.001	0.011	0.047
Increase in ejection fraction (per 5 percentage points increase)	0.61 (0.50, 0.73)	0.60 (0.50, 0.72)	0.67 (0.50, 0.90)	0.69 (0.51, 0.93)
P	<0.001	<0.001	0.007	0.014

MADIT-CRT: LEFT ATRIUM AND SUBSEQUNT CLINICAL OUTCOME

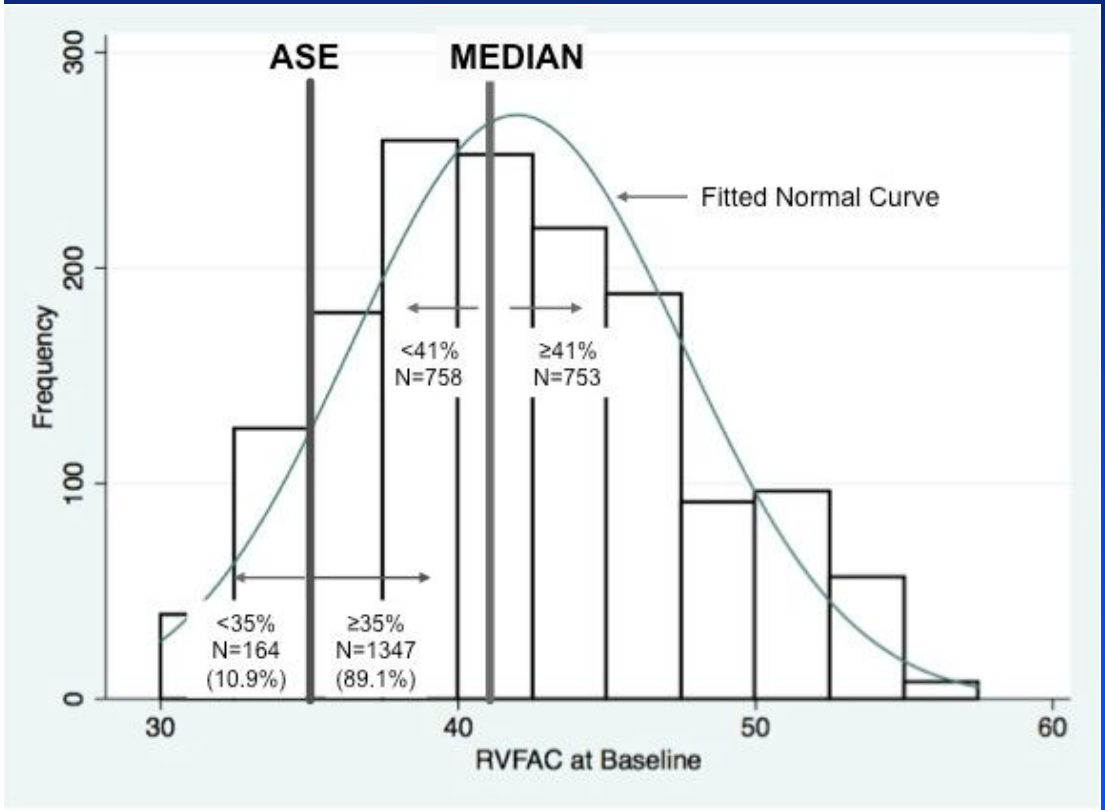
Goldenberg et al. Unpublished

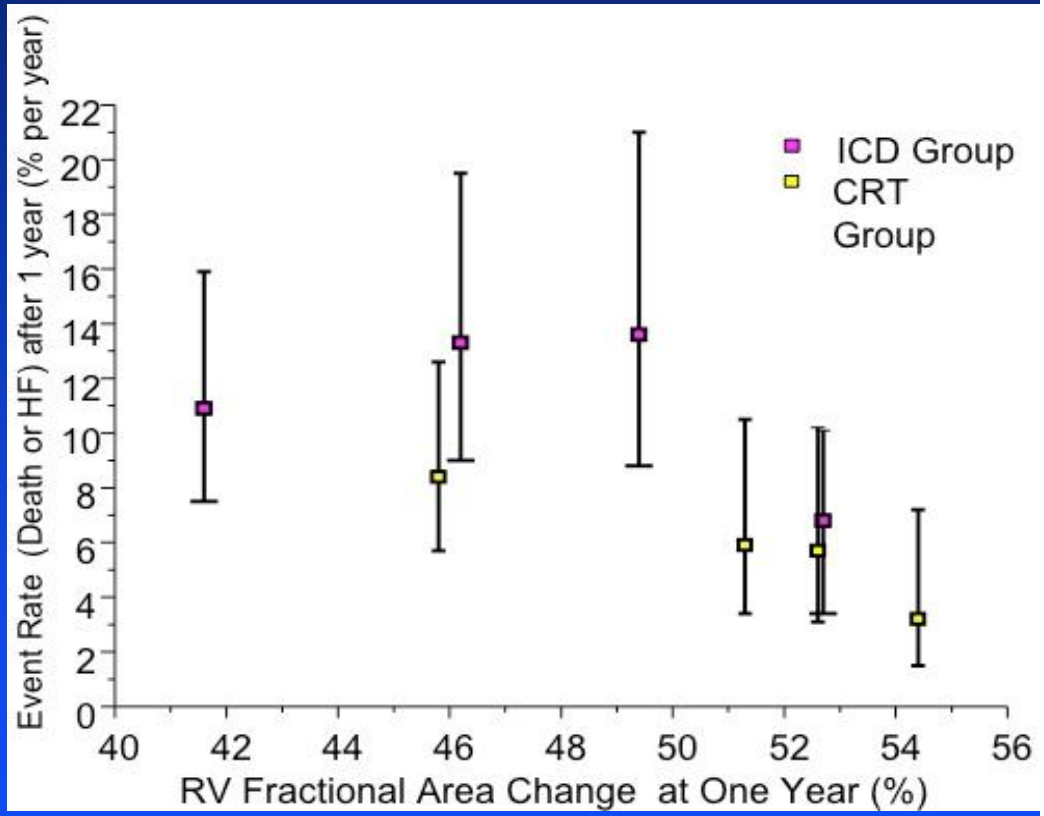




MADIT-CRT: RIGHT VENTRICLAR REMODELING

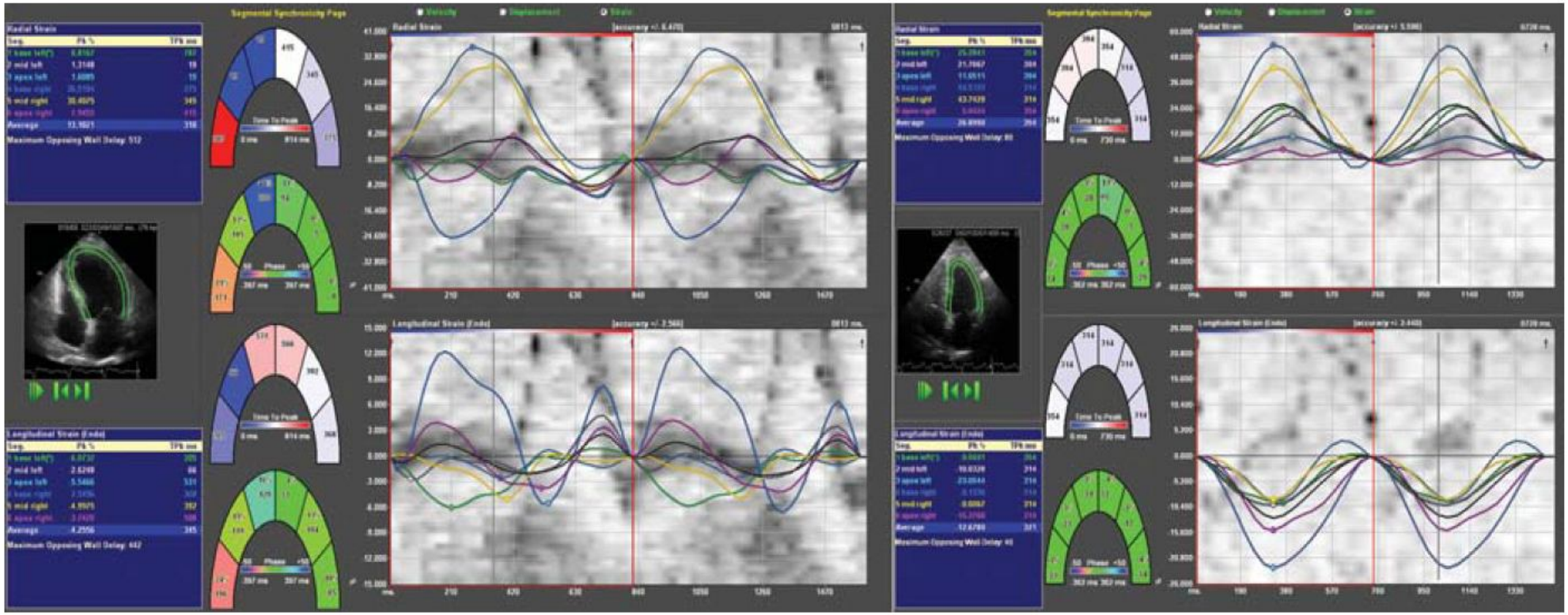
Solomon et al et al. Circulation HF, 2012





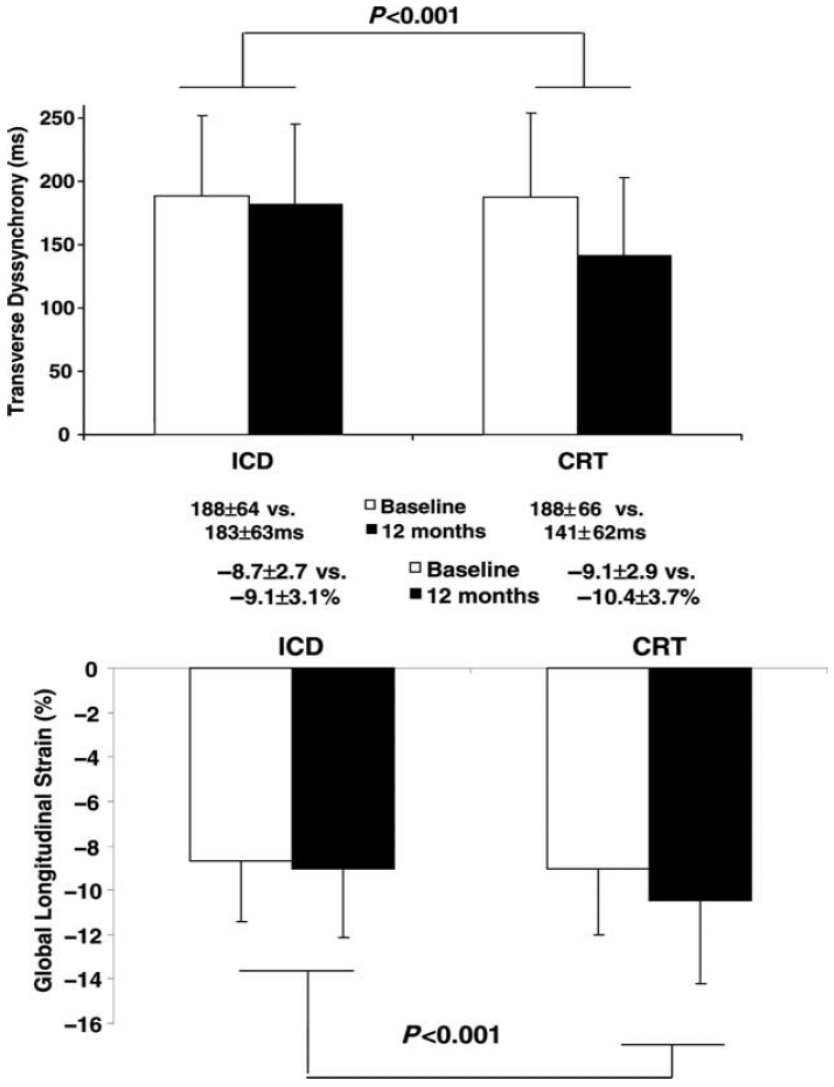
MADIT-CRT: DYSSYNCHRONY

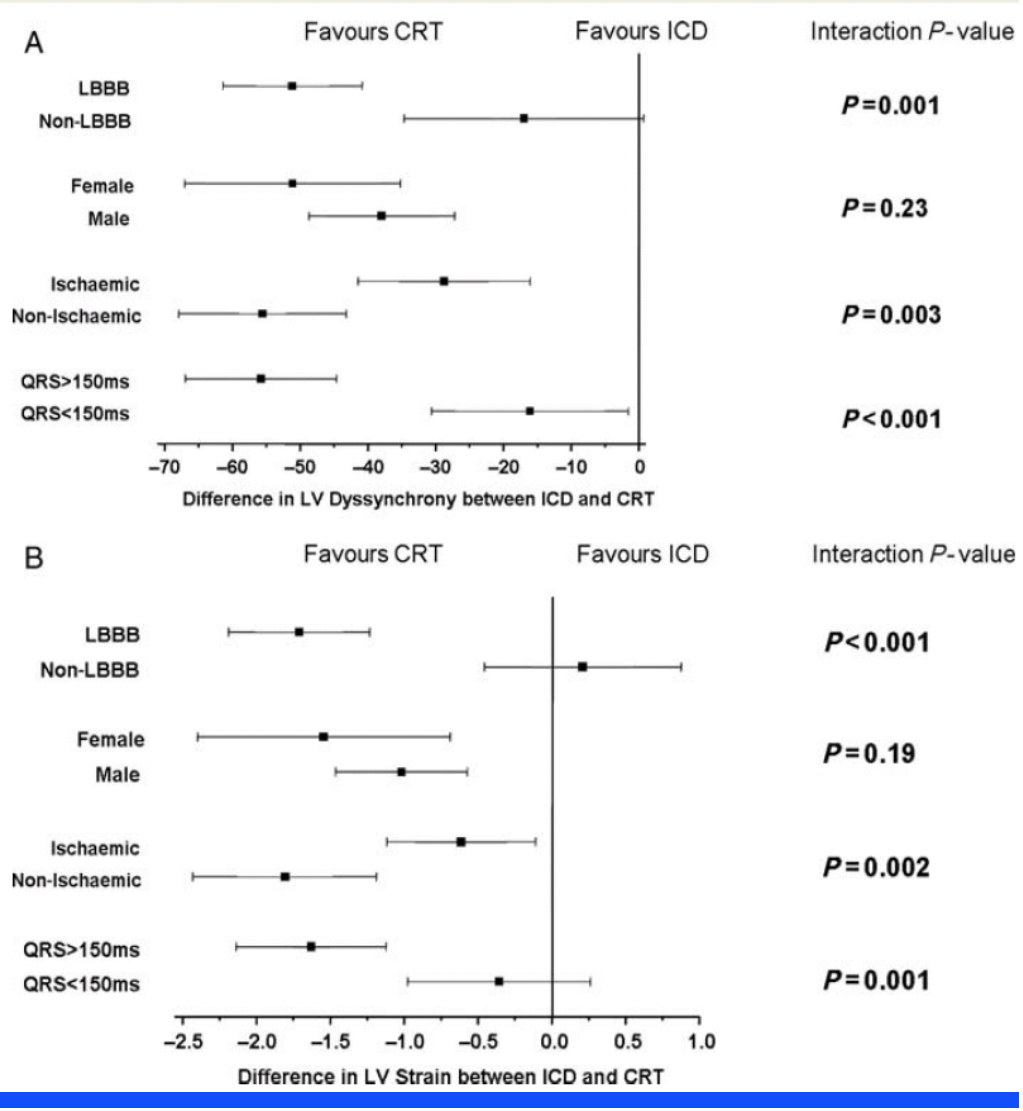
Solomon et al. European Heart Journal, 2011



MADIT-CRT: DYSSYNCHRONY

Solomon et al et al. European Heart Journal, 2011

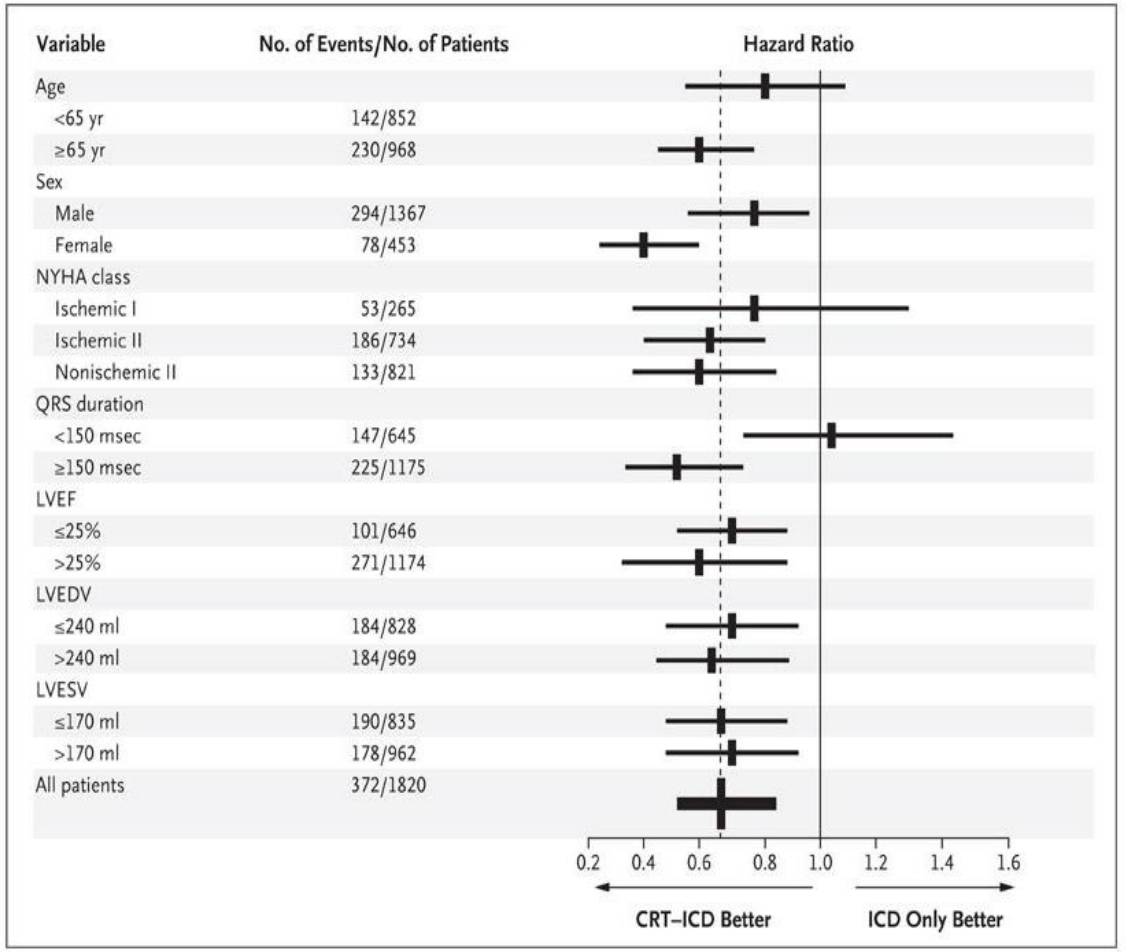




CLINICAL EFFICACY IN SUBGROUPS

MADIT-CRT: SUBGROUP ANALYSIS
Moss et al. NEJM, 2009

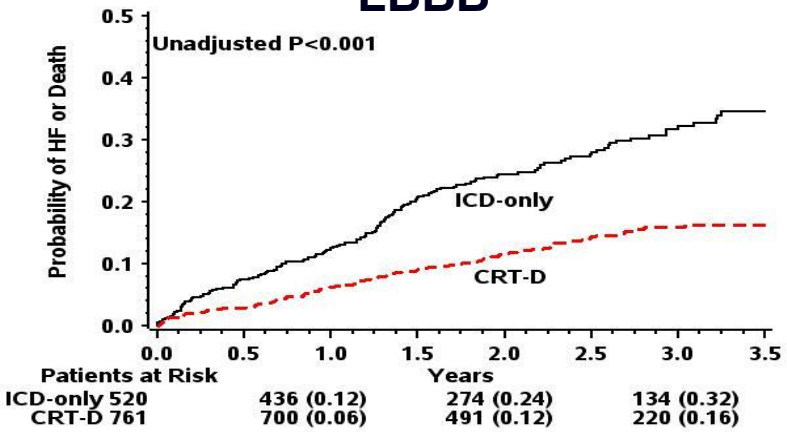
- **Differential clinical response:**
  - Gender
  - QRS duration
- **Differential echo response:**
  - ↗ Ischemic vs. non ischemic CMP



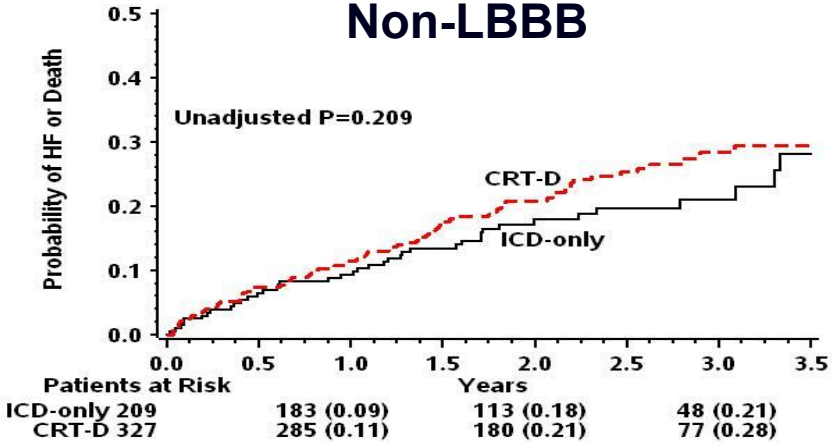
MADIT-CRT: QRS MORPHOLOGY

Zareba et al. Circulation , 2011

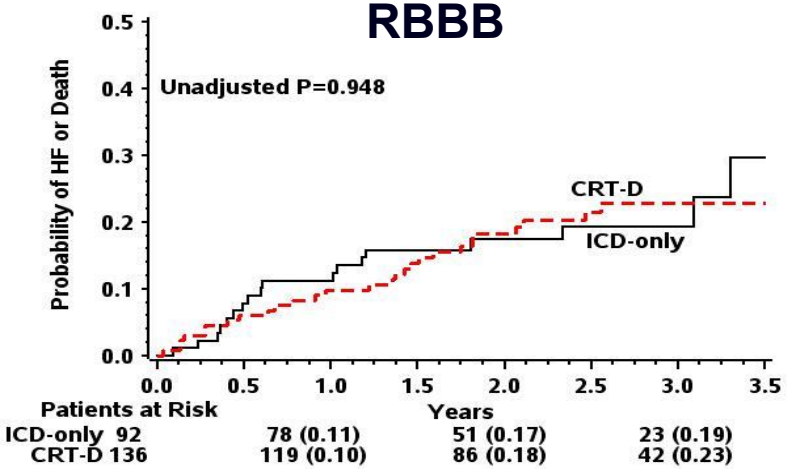
LBBB



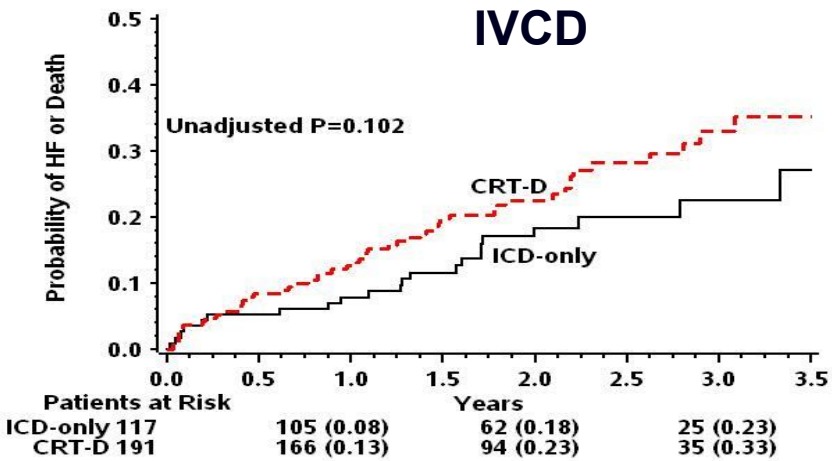
Non-LBBB



RBBB

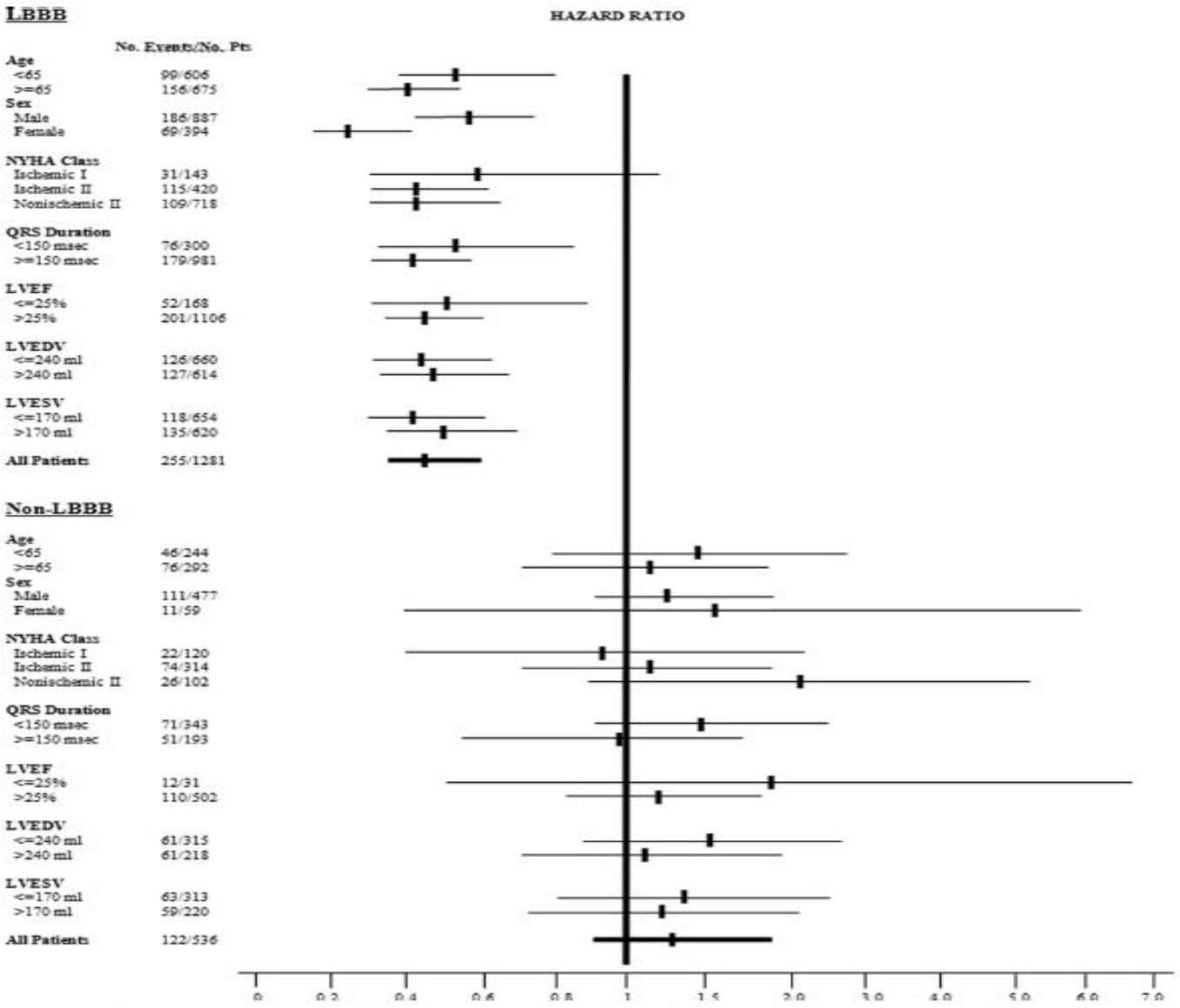


IVCD



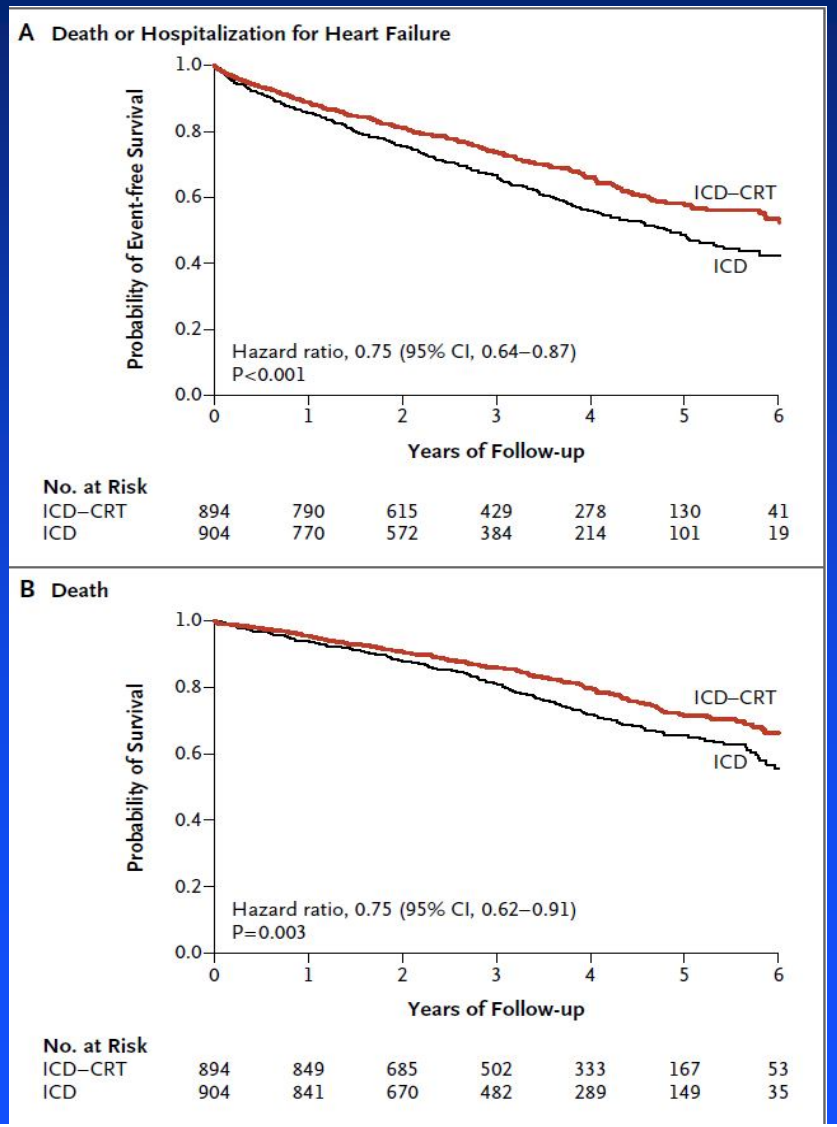
MADIT-CRT: QRS MORPHOLOGY

Zareba et al. Circulation , 2011



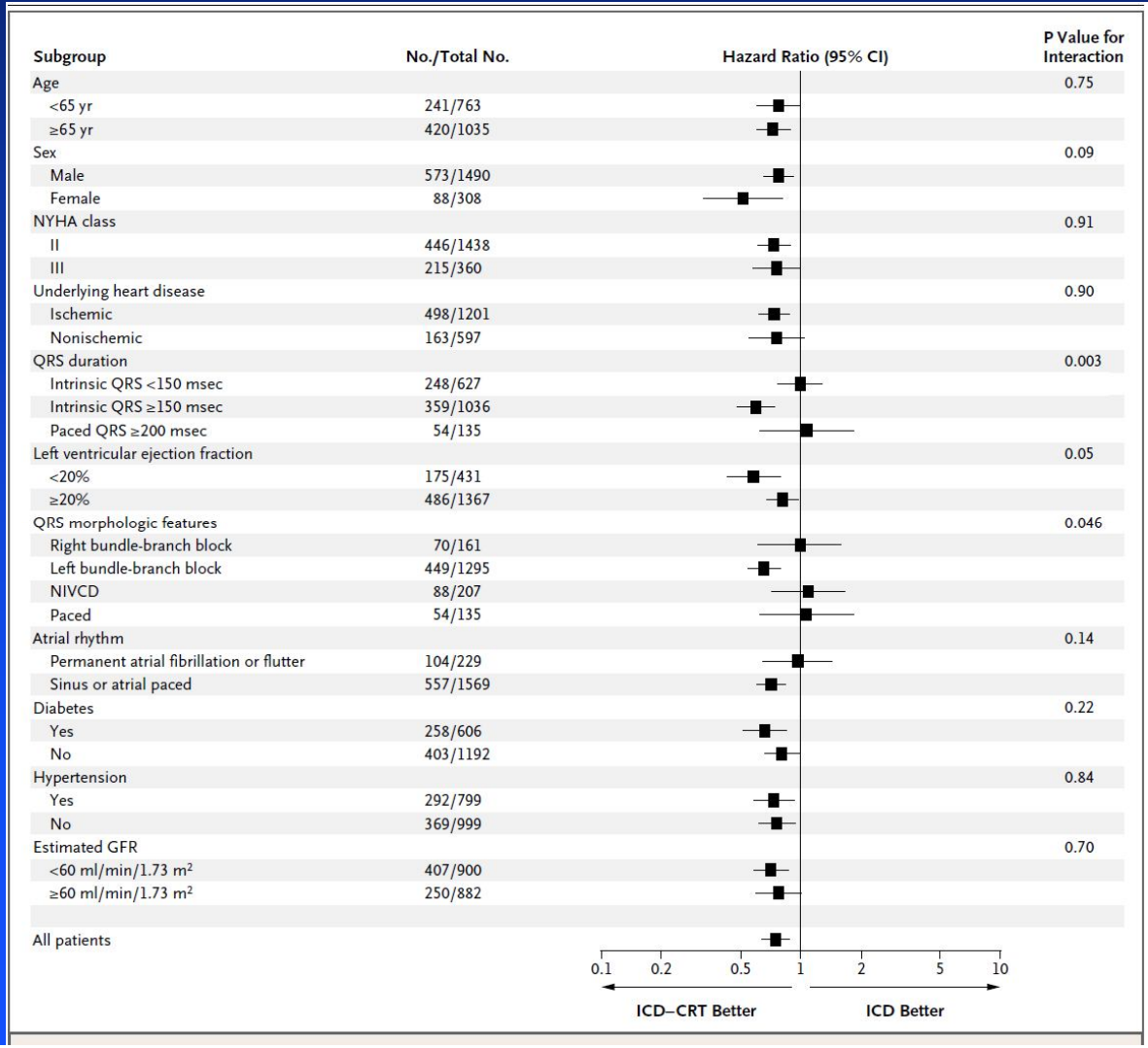
RAFT
Tang et al. NEJM, 2010

- **1798 ICM/NICM pts:**
  - EF ≤ 30%
  - QRS ≥ 120 msec
  - NYHA II/III
- **Randomization:**
  - CRT-D vs. ICD-only
  - 1:1 ratio
- **Outcome:**
  - HR=0.68 (p<0.001)



RAFT: SUBGROUP ANALYSIS
Tang et al. NEJM, 2010

- **Differences in clinical response:**
  - **QRS duration**
  - **QRS morphology**
  - **Gender**



2012 UPDATED GUIDELINES

CLASS I

1. **CRT is indicated for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and NYHA class II, (546,547) III, or ambulatory IV (542–545); symptoms on GDMT. *(Level of Evidence: A for NYHA class III/IV; Level of Evidence: B for NYHA class II)***

CLASS IIa

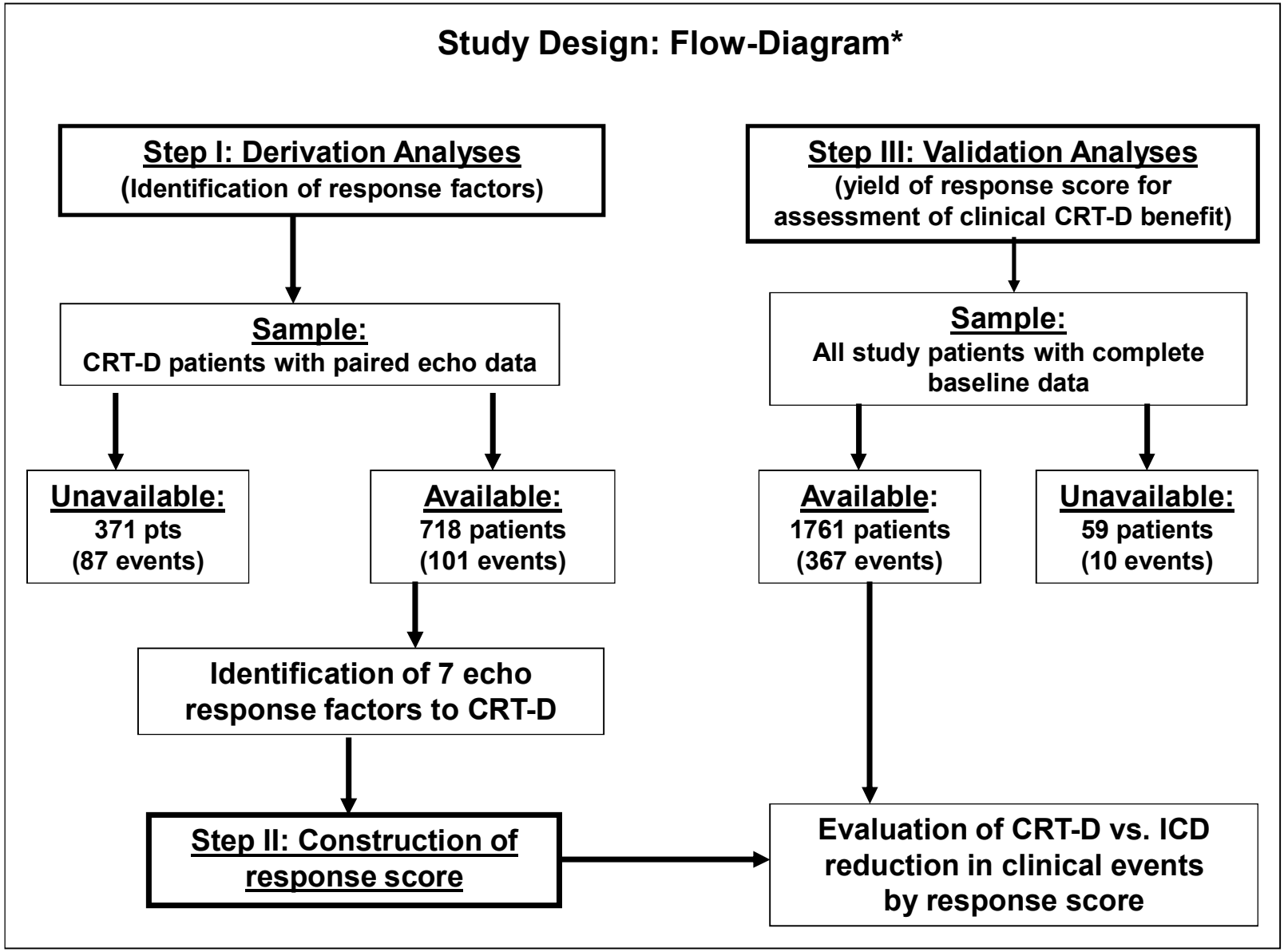
1. **CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT (542–544,546–548). (*Level of Evidence: B*)**
2. **CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ ambulatory class IV symptoms on GDMT (542–544,547). (*Level of Evidence: A*)**

PREDICTORS OF RESPONSE IN MADIT-CRT

Goldenberg et al. Circulation, 2011

- *Individual factors may contribute differently to the clinical response to CRT*
- *Echocardiographic response correlated with clinical response in MADIT-CRT*
- *Combined assessment of factors associated with a favorable echo response can identify patients who derive clinical benefit from CRT-D*

STUDY DESIGN



STEP I: FACTORS ASSOCIATED WITH ECHO RESPONSE TO CRT-D*

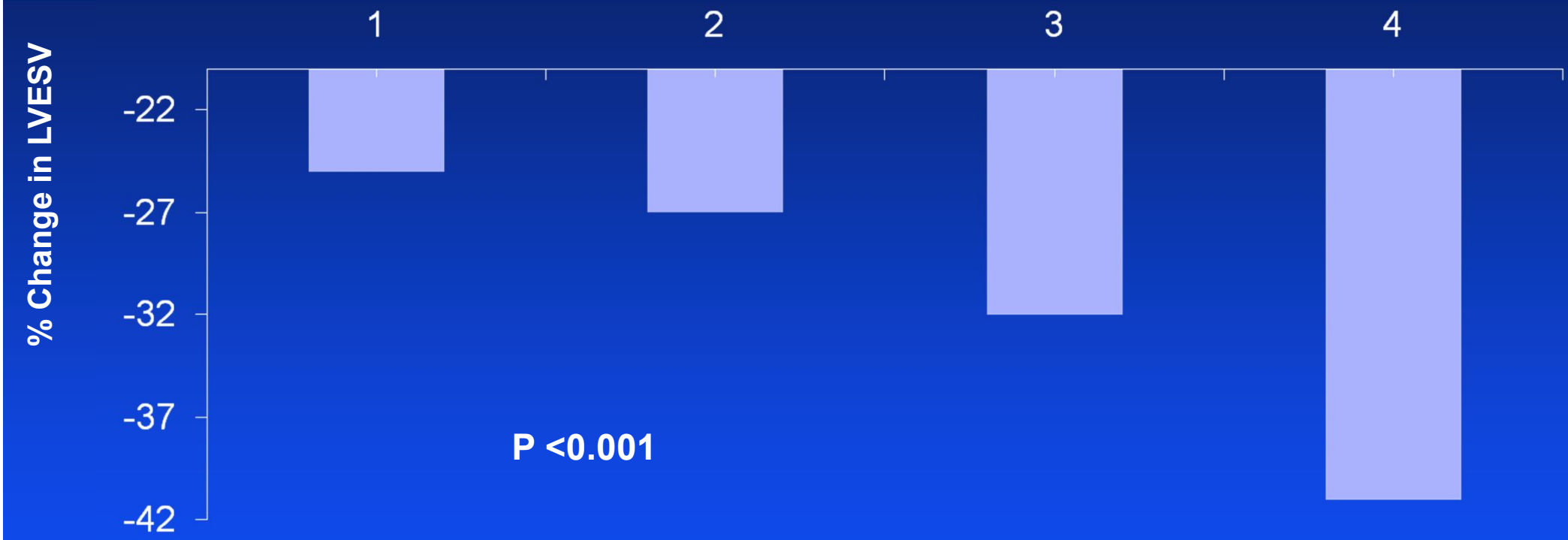
	Incremental Response (SE)	P-value	Score
Female	-2.9% (1.0%)	0.003	2
Non-ischemic	-4.2% (0.9%)	<0.001	2
QRS ≥ 150 msec	-2.7% (0.9%)	0.003	2
LBBB	-3.4% (1.0%)	<0.001	2
Prior HF hospitalization	-1.9% (0.8%)	0.02	1
Baseline LAV <40 ml/m^2	-4.2% (1.1%)	<0.001	3
Baseline LVEDV ≥ 125 ml/m^2	-5.6% (1.0%)	<0.001	2

*Results are obtained from a best subsets analysis that included 25 prespecified clinical and echocardiographic candidate factors

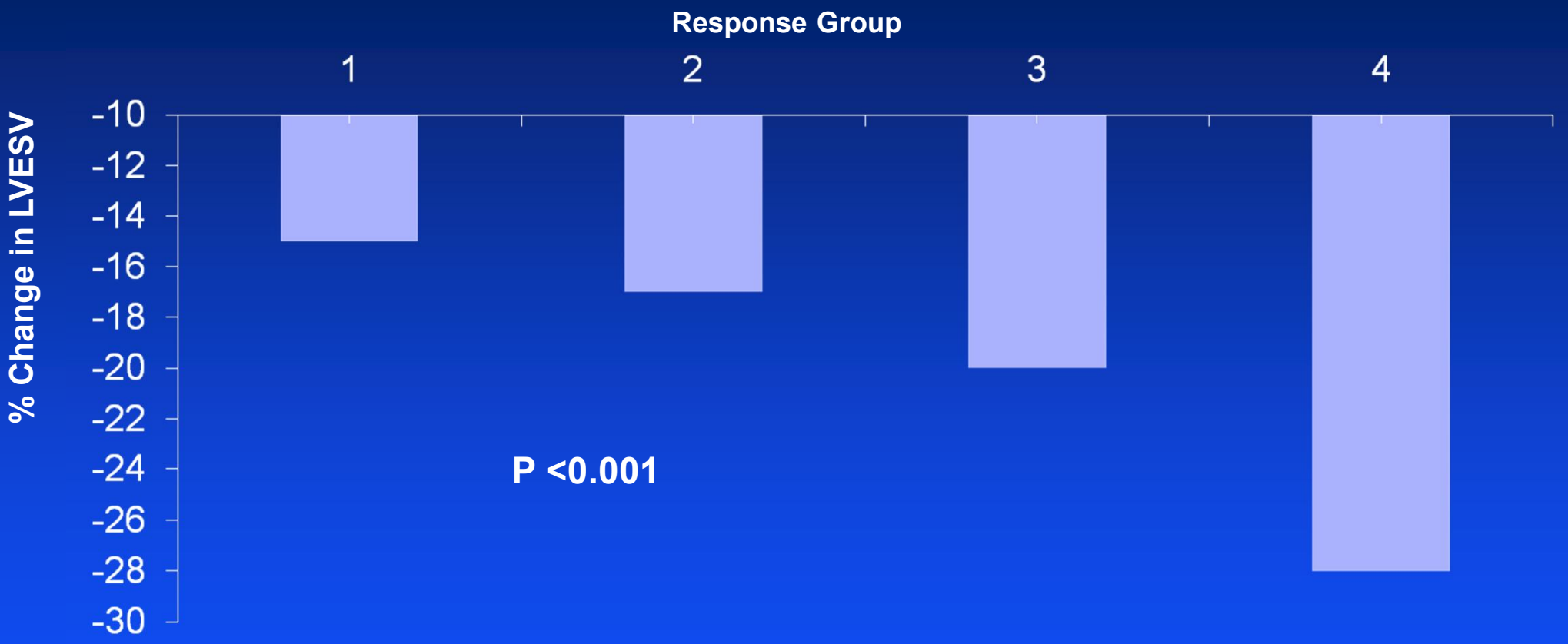
STEP II: CONSTRUCTION OF RESPONSE SCORE

- Response score range 0 to 14
- Pts categorized into approximate quartiles based on the distribution of the response scores:
  - Group 1 (n=391): Q1 score 0-4
  - Group 2 (n=401): Q2 score 5-6
  - Group 3 (n=469): Q3 score 7-8
  - Group 4 (n=500): Q4 score 9-14

PERCENT CHANGE IN LVEDV BY RESPONSE GROUP

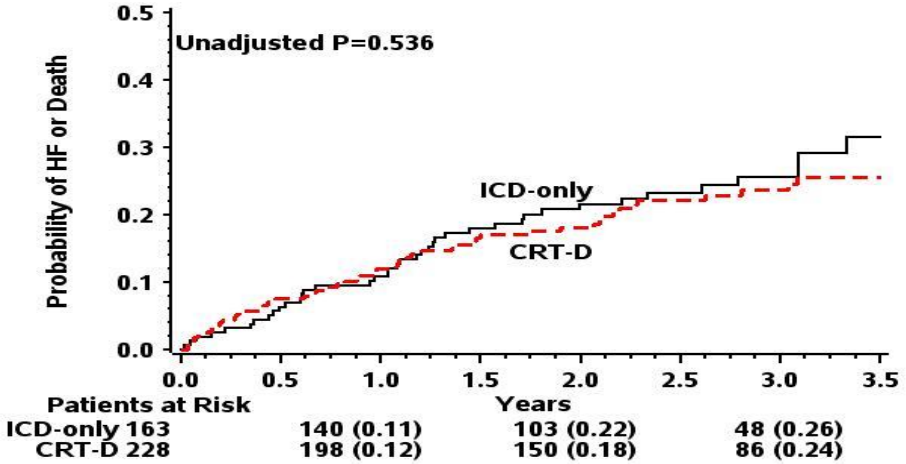


PERCENT CHANGE IN LVESV BY RESPONSE GROUP

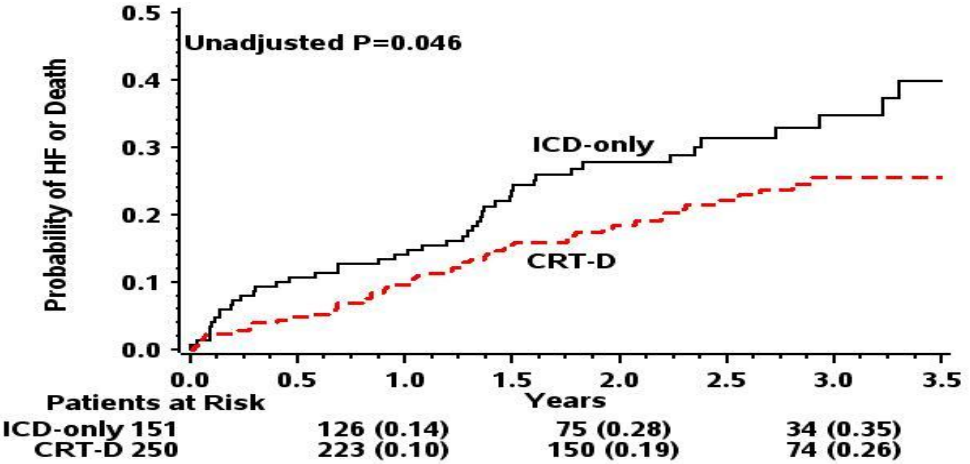


CLINICAL BENEFIT BY SCORE GROUP

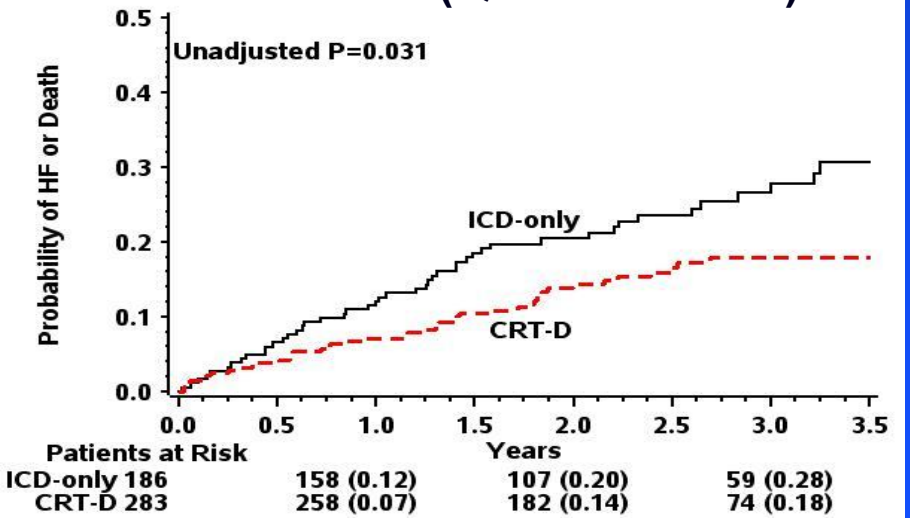
GROUP 1 (Q1 SCORE: 0-4)



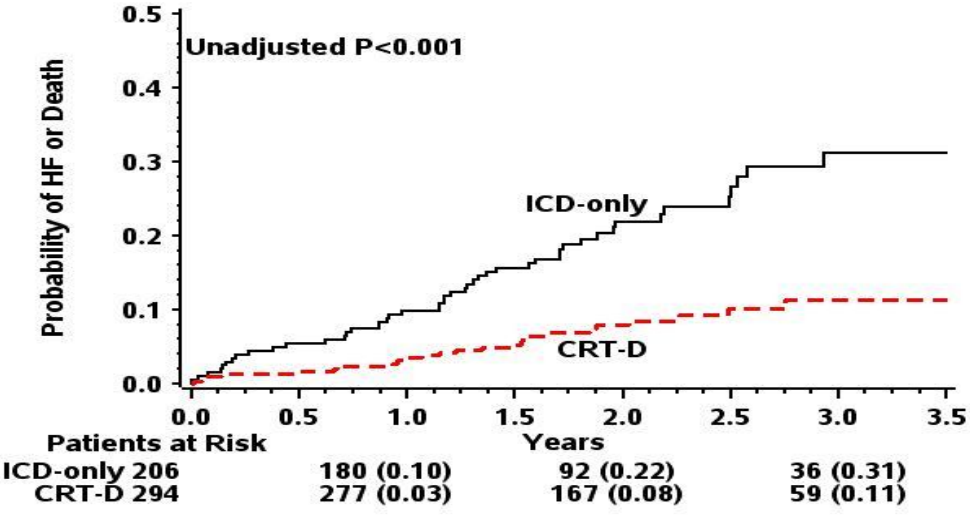
GROUP 2 (Q2 SCORE: 5-6)



GROUP 3 (Q3 SCORE 7-8)

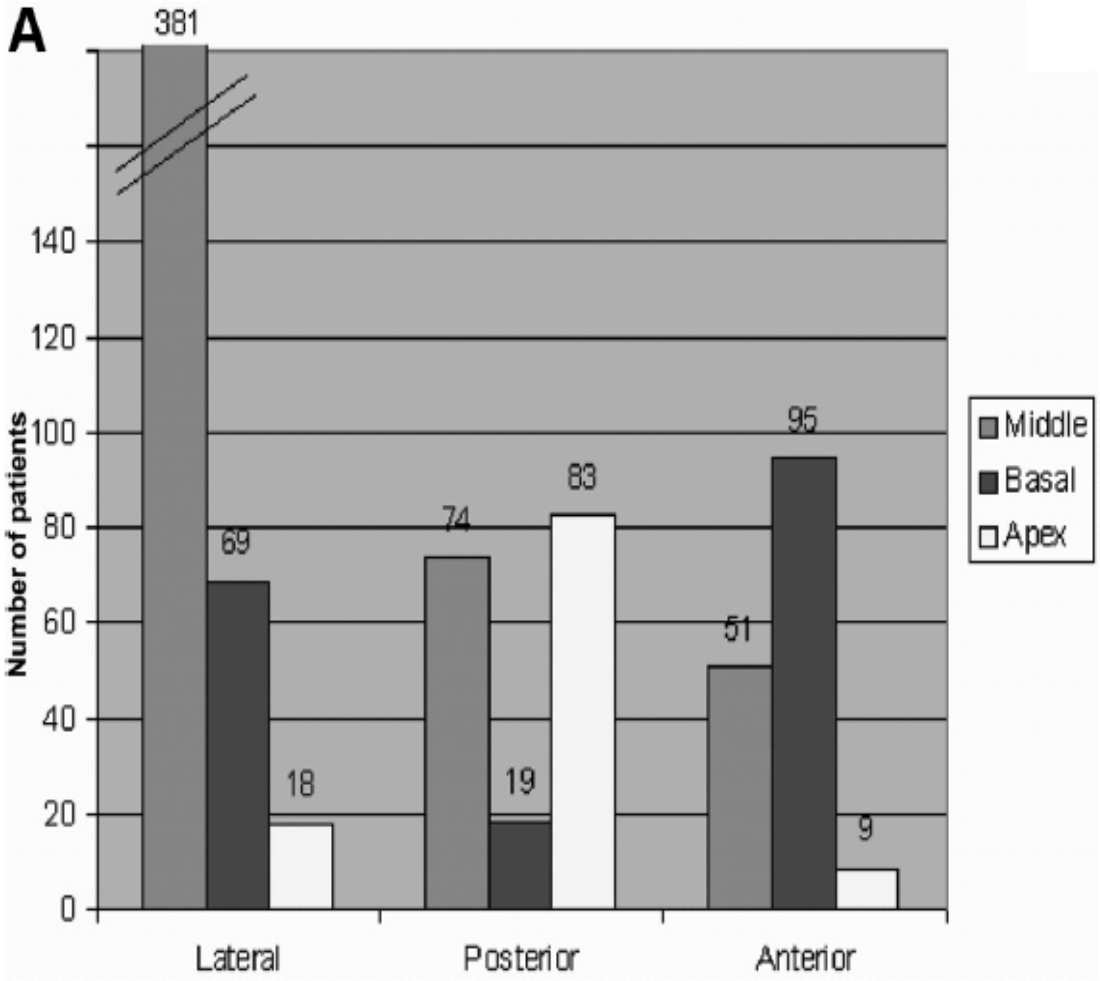


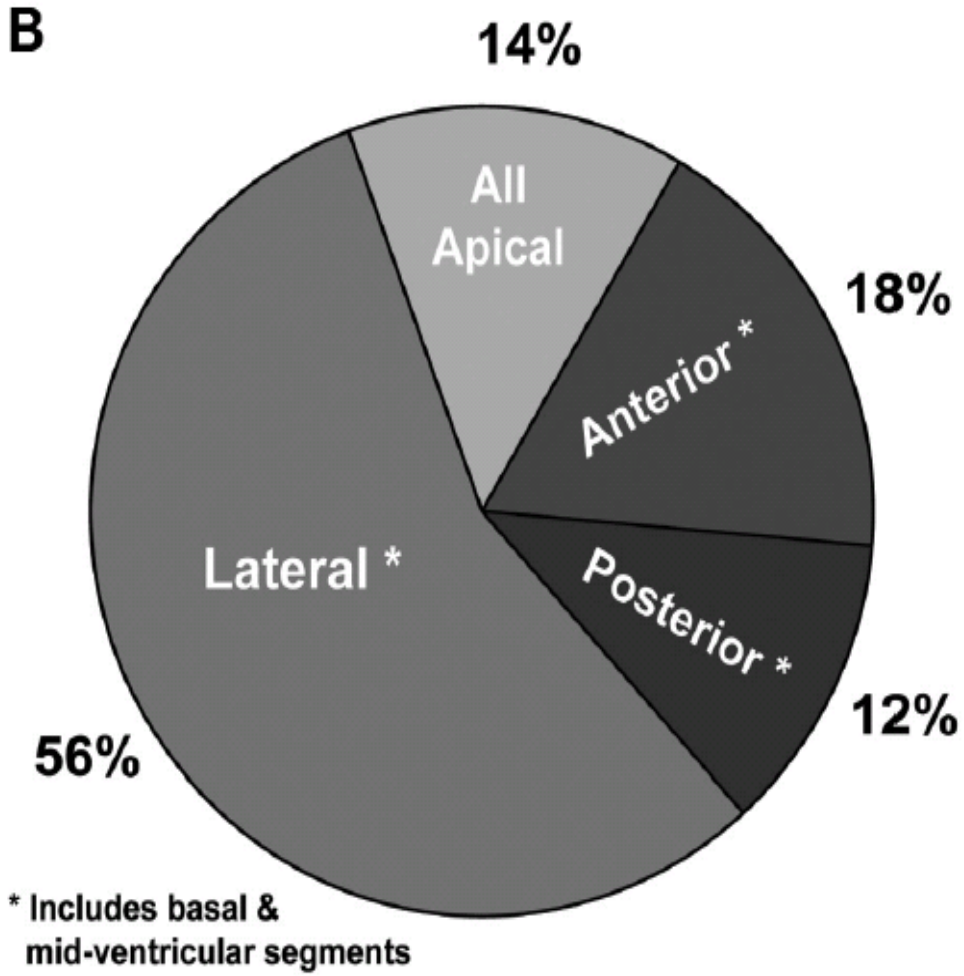
GROUP 4 (Q4 SCORE ≥9)



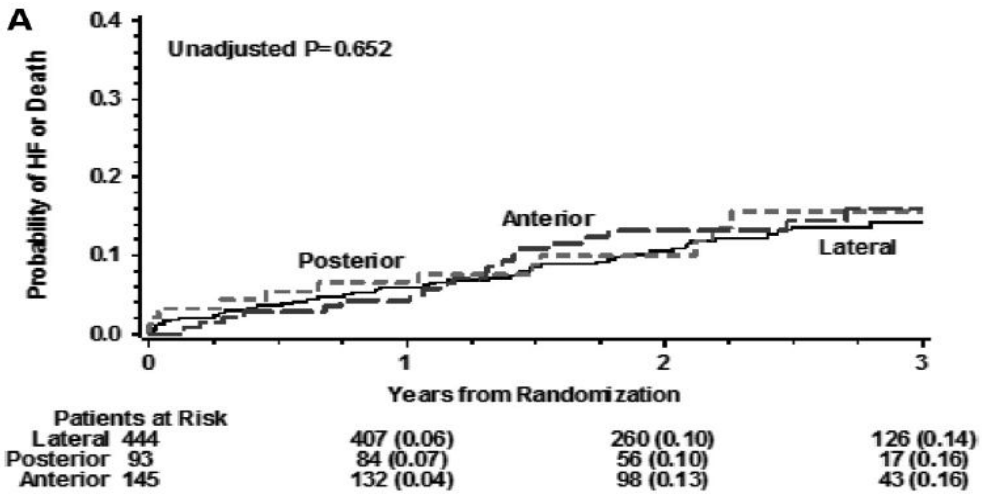
Response Groups	Score	CRT-D vs ICD-Only Risk of HF or Death			*P* for Trend†
		HR	95% CI	*P*	
All patients (n=1761)	0–14	0.62	0.51–0.77	<0.001	NA
By response score quartile					
1 (n=391)	0–4	0.87	0.58–1.32	0.52	0.005
2 (n=401)	5–6	0.67	0.46–0.98	0.04	
3 (n=469)	7–8	0.64	0.43–0.97	0.03	
4 (n=500)‡	≥9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

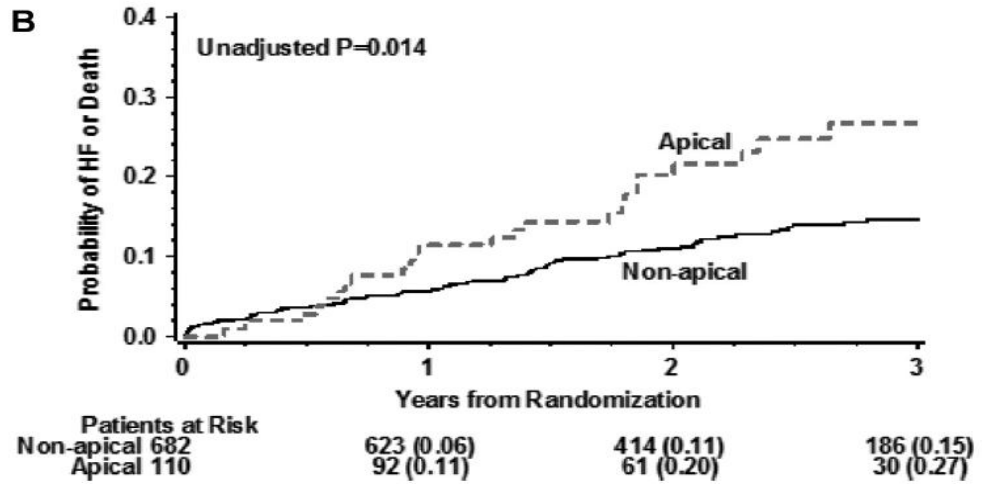
LEAD POSITION IN MADIT-CRT
Singh et al. Circulation 2011





LEAD POSITION IN MADIT-CRT
Singh et al. Circulation 2011





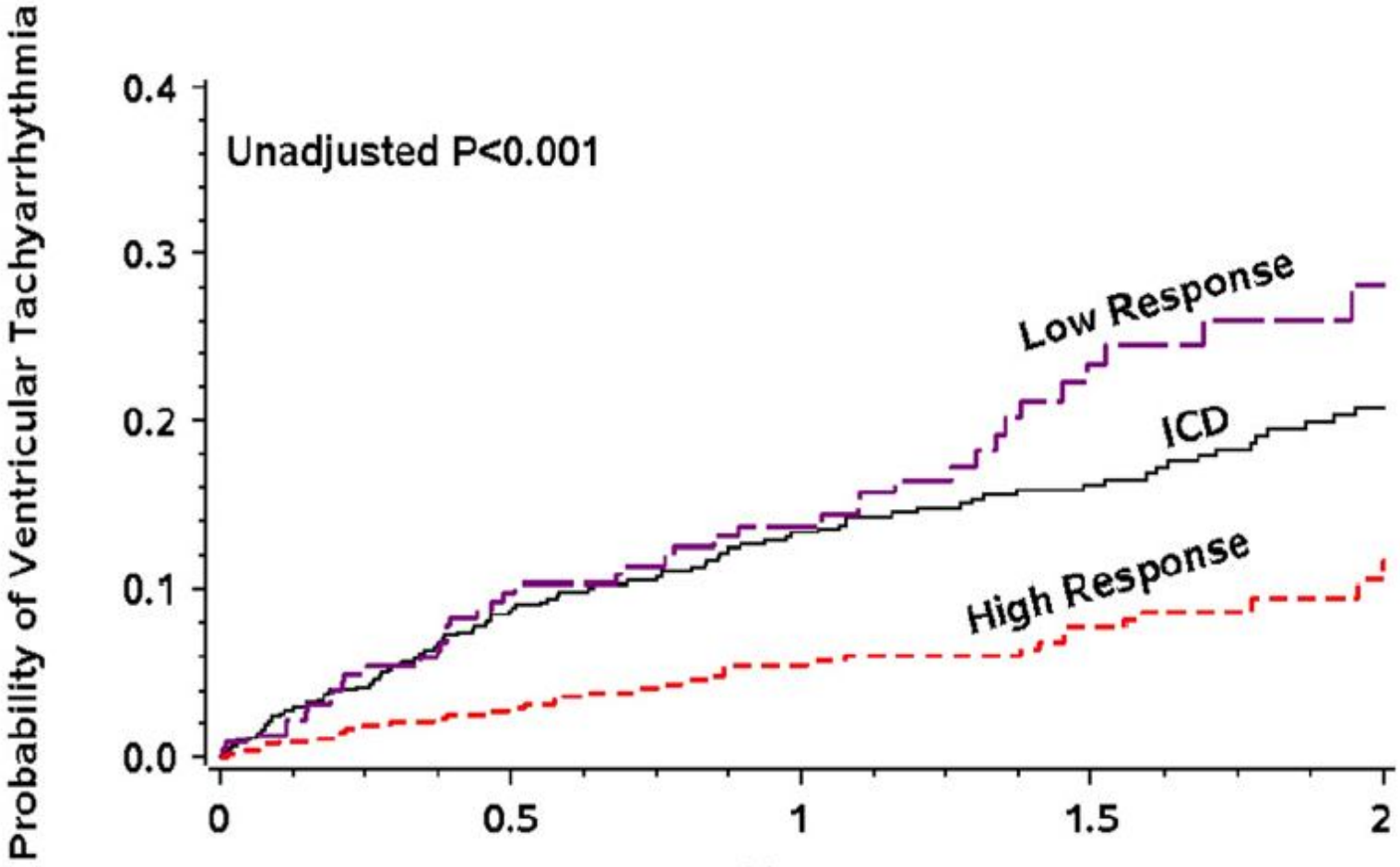
Heart failure only	Apical vs nonapical	1.55 (0.94–2.53)	0.083
	Apical vs basal	2.20 (1.15–4.21)	0.018
	Apical vs midventricular	1.38 (0.83–2.28)	0.214
	Midventricular vs basal	1.60 (0.94–2.72)	0.086
	Posterior vs anterior	1.11 (0.53–2.29)	0.787
	Lateral vs anterior	0.99 (0.58–1.67)	0.985
Death	Apical vs nonapical	2.91 (1.42–5.97)	0.004*
	Apical vs basal	5.27 (1.67–16.66)	0.005*
	Apical vs midventricular	2.45 (1.17–5.14)	0.018*
	Midventricular vs basal	2.15 (0.74–6.27)	0.161
	Posterior vs anterior	0.51 (0.11–2.47)	0.404
	Lateral vs anterior	0.79 (0.33–1.93)	0.606

LEAD POSITION IN MADIT-CRT
Limitations

- *No difference in echo response (somewhat better in apical)*
- *110 pts with apical lead position; 24 HF/death events*
- *Endpoint driven primarily by mortality (total=10; noncardiac =4)*
- *Within CRT-D difference, without comparison to ICD group*

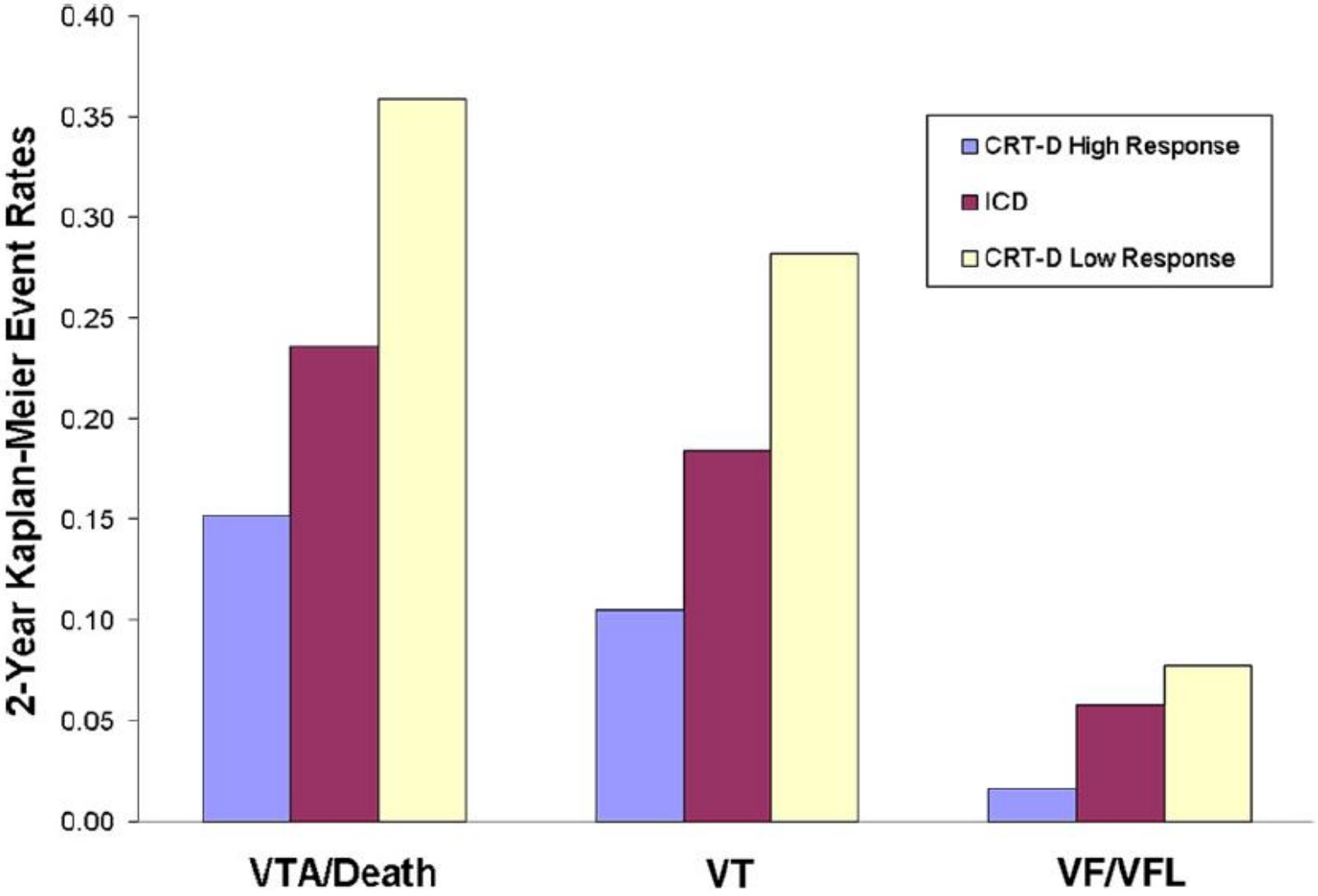
EFFECT ON ARRHYTHMIAS

REVERSE LV REMODELING AND SUBSEQUENT VENTRICULAR TACHYARRHYTHMIAS; *Barsehshet/Goldenberg et al. JACC 2011*

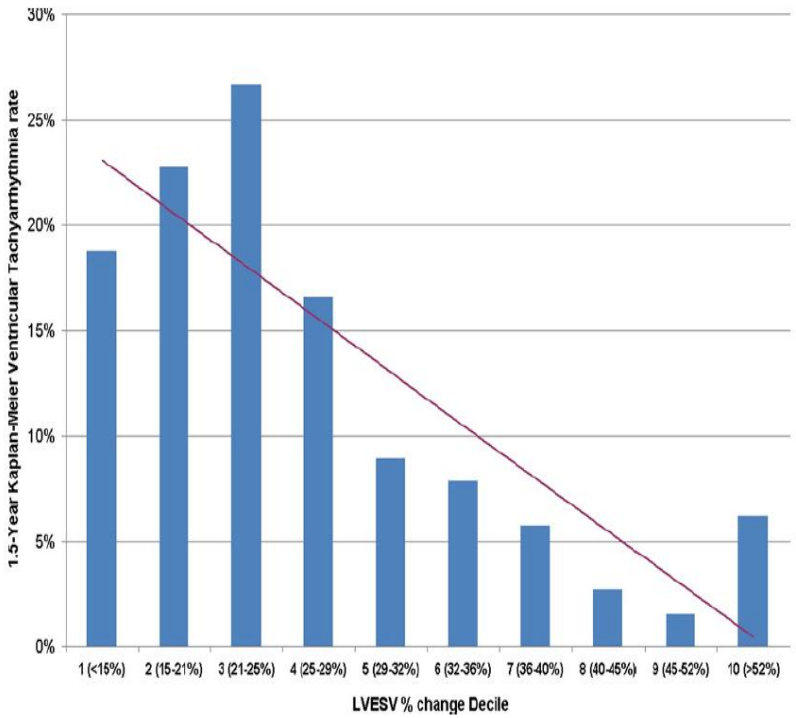


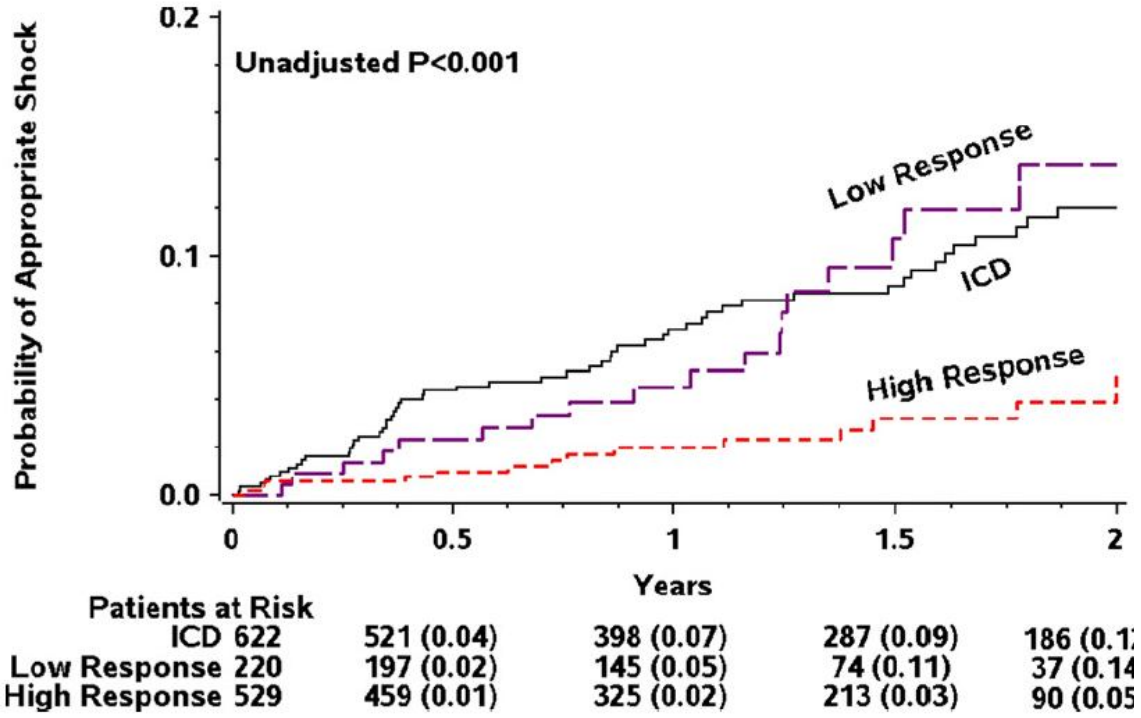
Patients at Risk				
ICD 622	497 (0.09)	371 (0.13)	263 (0.16)	166 (0.21)
Low Response 220	182 (0.10)	135 (0.14)	67 (0.23)	30 (0.28)
High Response 529	451 (0.03)	316 (0.05)	203 (0.08)	80 (0.12)

REVERSE LV REMODELING AND SUBSEQUENT VENTRICULAR TACHYARRHYTHMIAS; *Barsehshet/Goldenberg et al. JACC 2011*

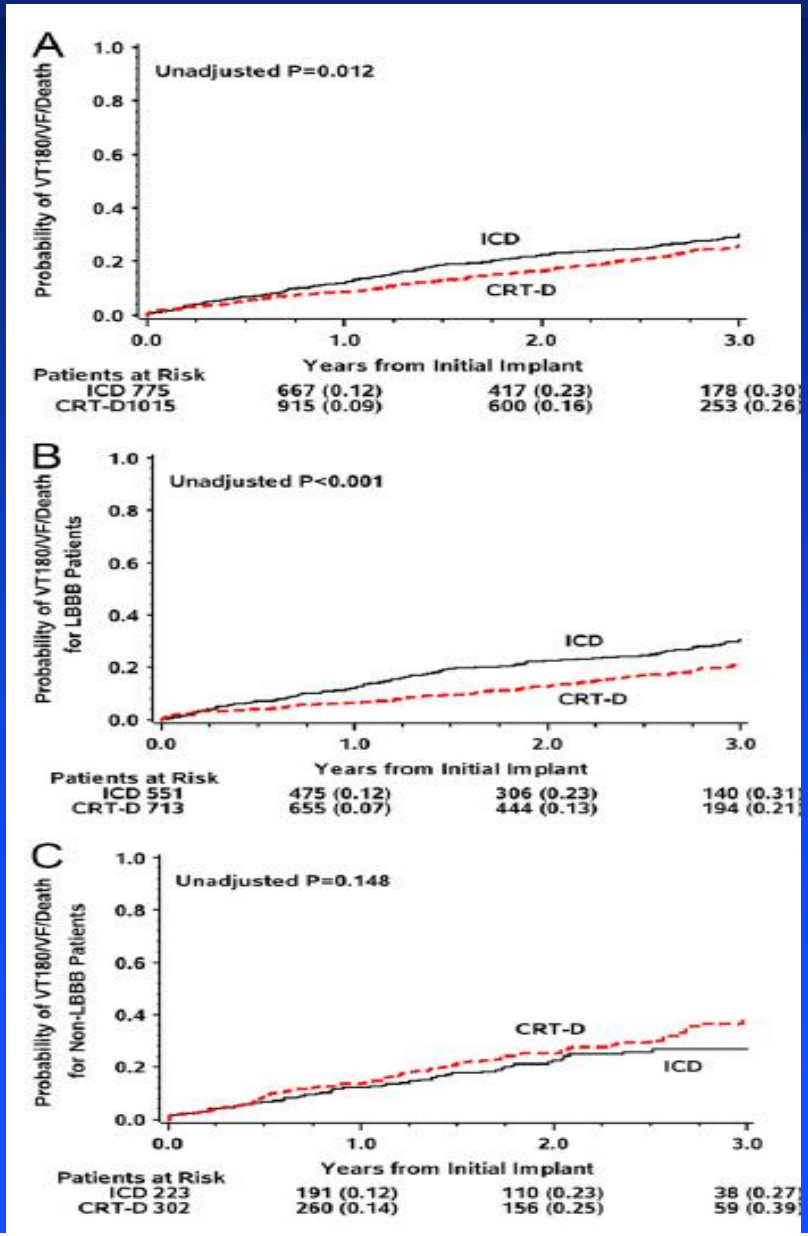


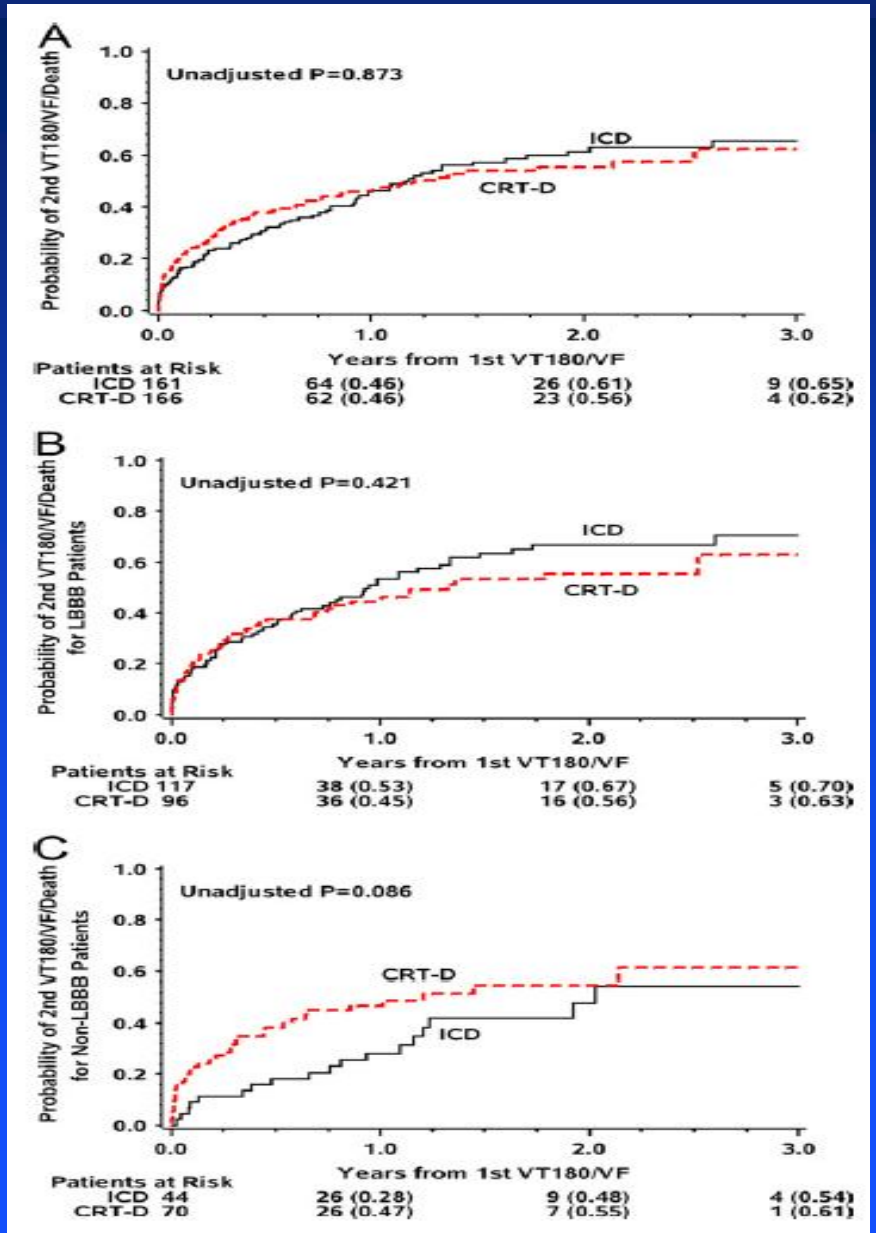
REVERSE LV REMODELING AND SUBSEQUENT VENTRICULAR TACHYARRHYTHMIAS; *Barsehshet/Goldenberg et al. JACC 2011*





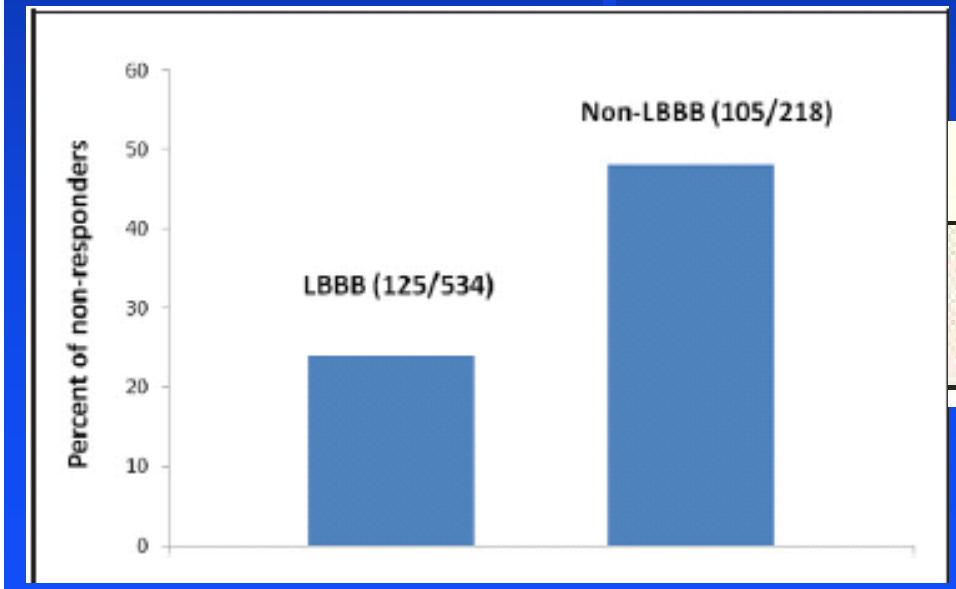
RECURRENT VENTRICULAR TACHYARRHYTHMIAS;
Oullet/Goldenberg et al. JACC 2012





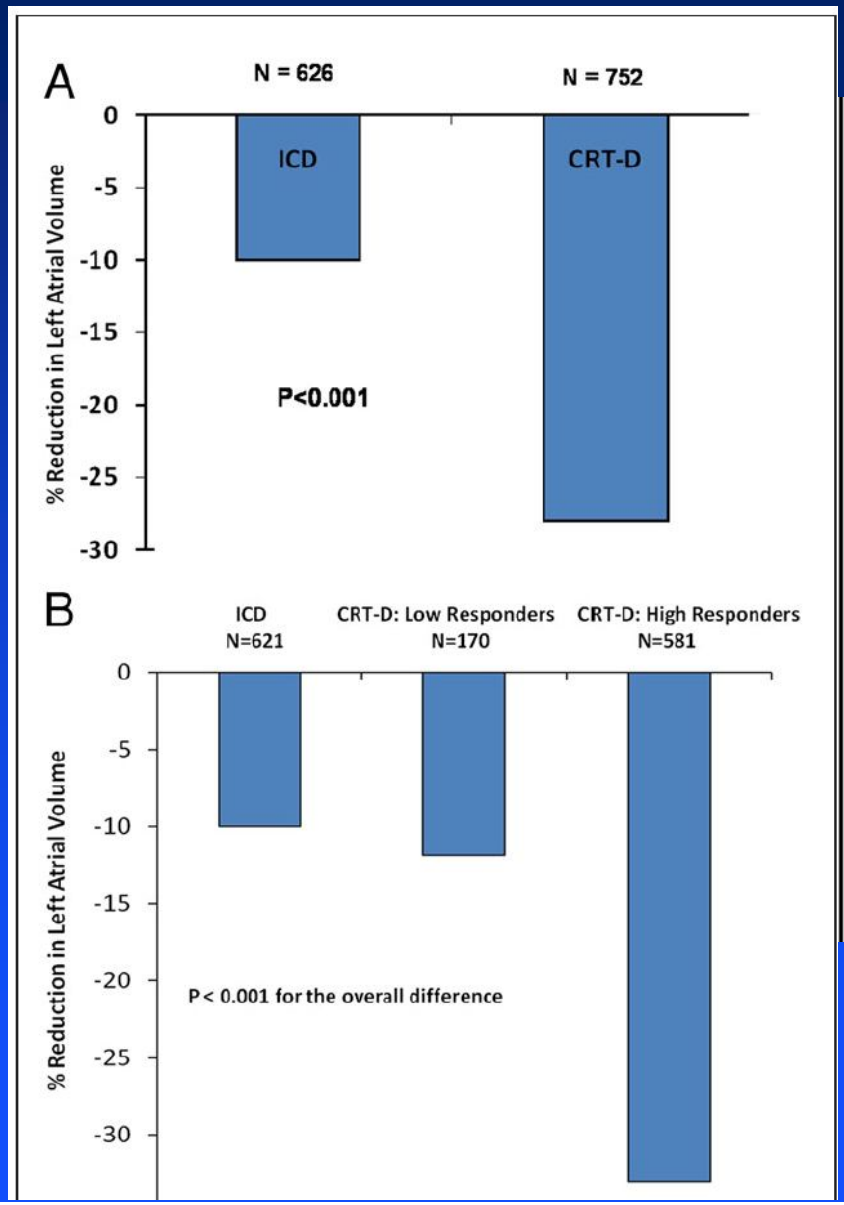
RECURRENT VENTRICULAR TACHYARRHYTHMIAS;
Oullet/Goldenberg et al. JACC 2012

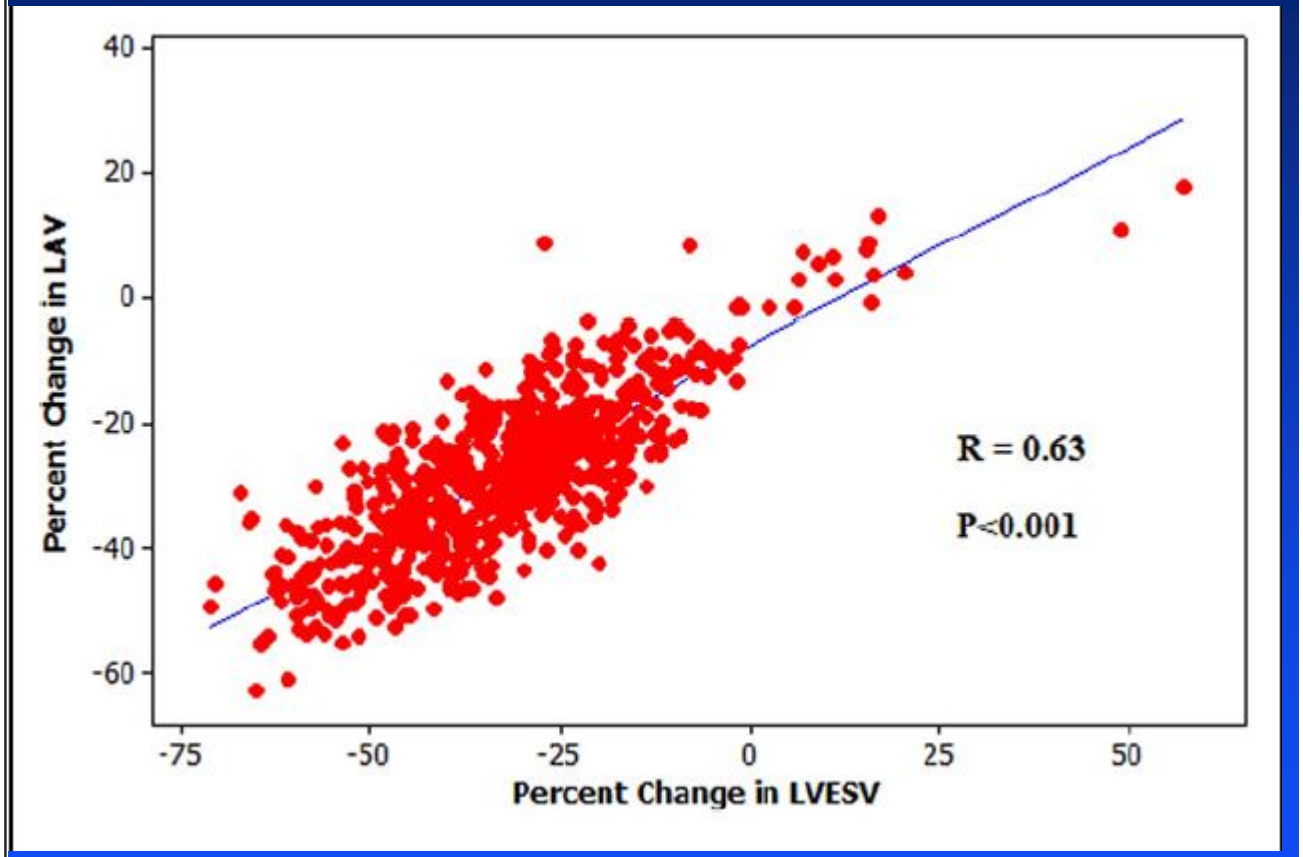
	All Patients		By QRS Morphology				
			LBBB Patients		Non-LBBB Patients		
Endpoint†	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	p Value for differen
First VTE (CRT-D vs. ICD)	0.71 (0.57–0.89)	0.003	0.58 (0.44–0.77)	<0.001	1.05 (0.71–1.54)	0.82	0.02
Subsequent VTEs (CRT-D vs. ICD)	1.58 (0.99–2.53)	0.05	0.98 (0.61–1.60)	0.95	3.62 (1.59–8.26)	0.002	0.009



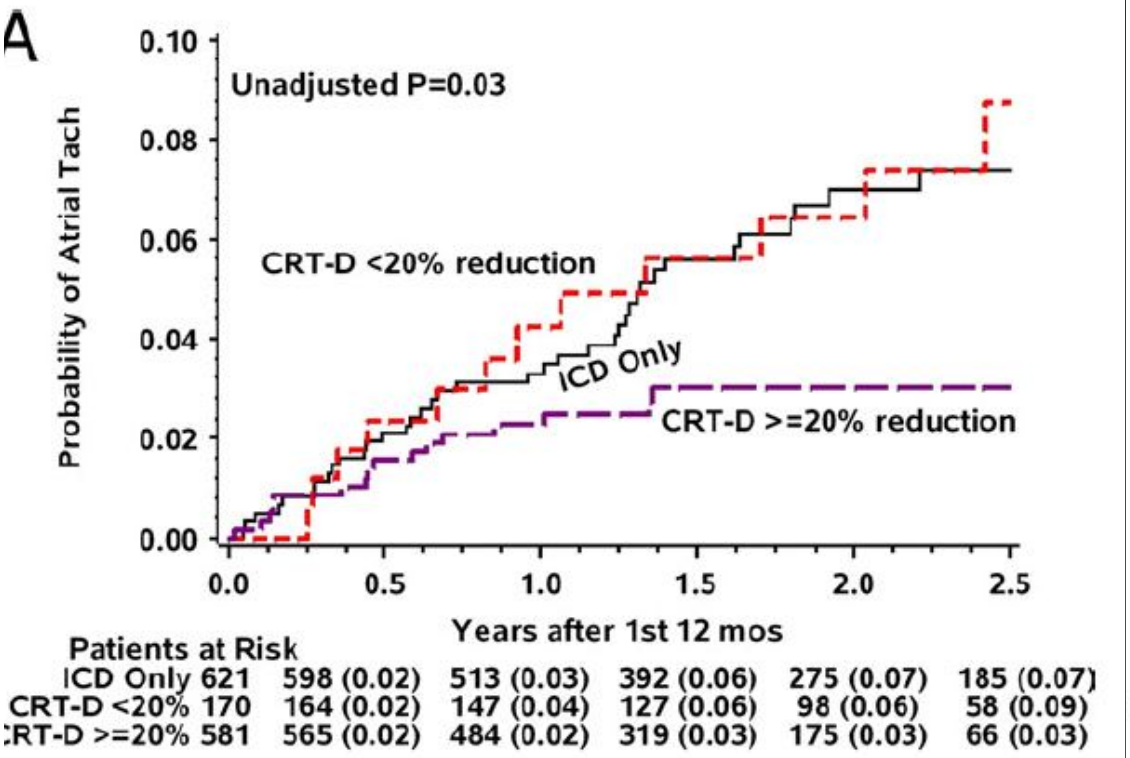
Treatment Effect	HR	95% CI	p Value
CRT-D responder* vs. ICD	0.54	0.42–0.68	<0.001
CRT-D nonresponder† vs. ICD	1.45	1.17–1.80	<0.001

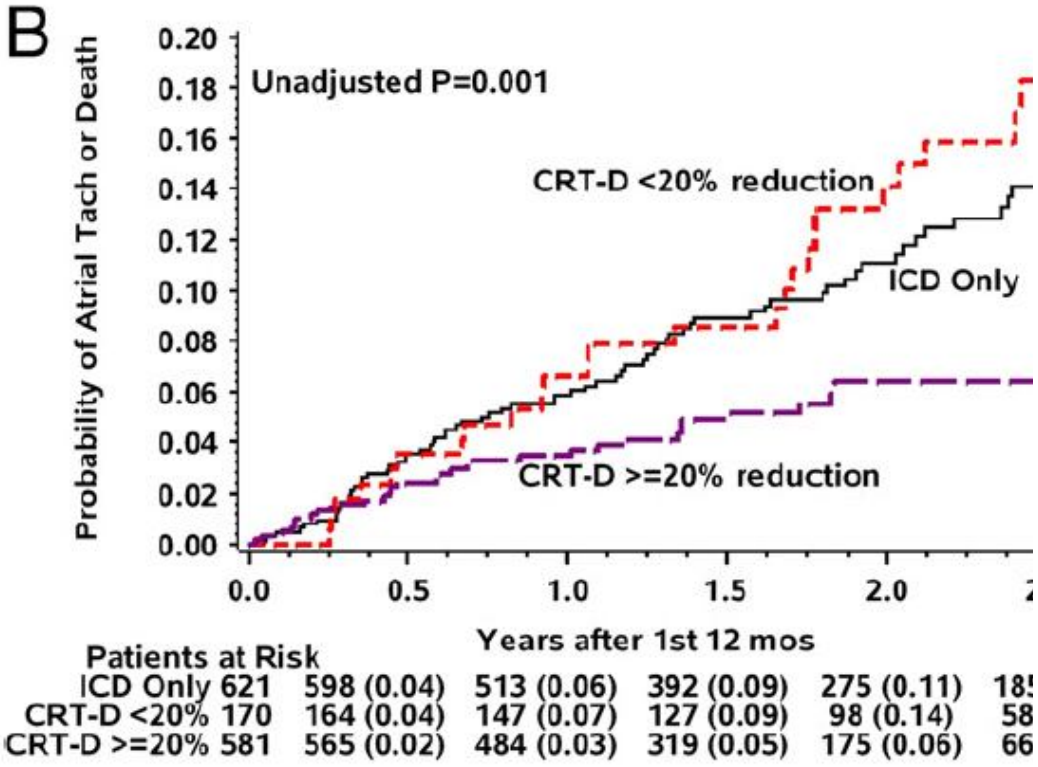
REVERSE LA REMODELING AND SUBSEQUENT ATRIAL TACHYARRHYTHMIAS; *Brenyo/Goldenberg et al. JACC 2011*





REVERSE LA REMODELING AND SUBSEQUENT ATRIAL TACHYARRHYTHMIAS; *Brenyo/Goldenberg et al. JACC 2011*





TAKE HOME MESSAGES: CRT IN MILD HF PTS

- Clinical benefit directly related to reverse remodeling of LV/LA
- No evidence for clinical benefit in non-LBBB pts
- No evidence for difference in efficacy within LBBB pts by QRS width
- Combined assessment can be used to identify enhanced responders
- Data regarding apical lead position require further validation

TAKE HOME MESSAGES: CRT IN MILD HF PTS

- Reverse remodeling effects on LV are directly related to reduced risk for ventricular tachyarrhythmias
- Reverse remodeling effects on LA are directly related to reduced risk for atrial tachyarrhythmias
- CRT may increase recurrent VA risk in non-LBBB patients (NYHA I/II)

Thank You