

CRT in Mild Heart Failure

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Aims

- History
- Mechanisms
- Background Studies Leading up to MADIT-CRT

Treatment of Heart Failure

18th Century : Digitalis Folia

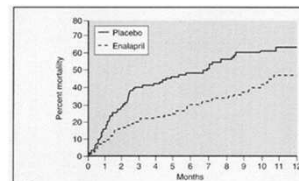
1920s : Mercurial Diuretics
1950s : Thiazide Diuretics
1960s : Loop Diuretics

1987 : ACE Inhibitors
1997 : Beta - Blockers
2000 : Spironolactone

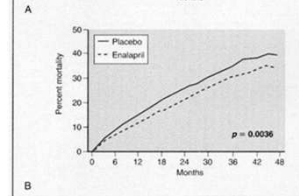


Consensus and SOLVD studies

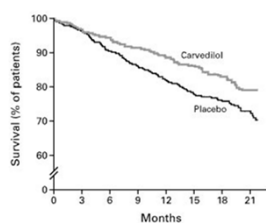
N Engl J Med.
1987 Jun
4;316(23):142-9-35



N Engl J Med.
1991 Aug
325 (5): 293-302



Effect of Carvedilol on Survival in Severe Chronic Heart Failure



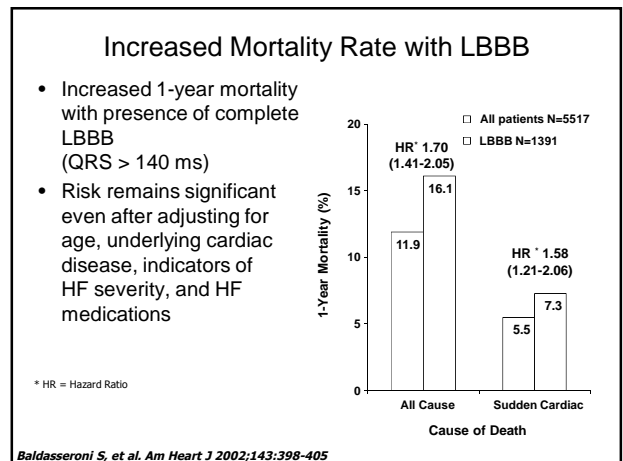
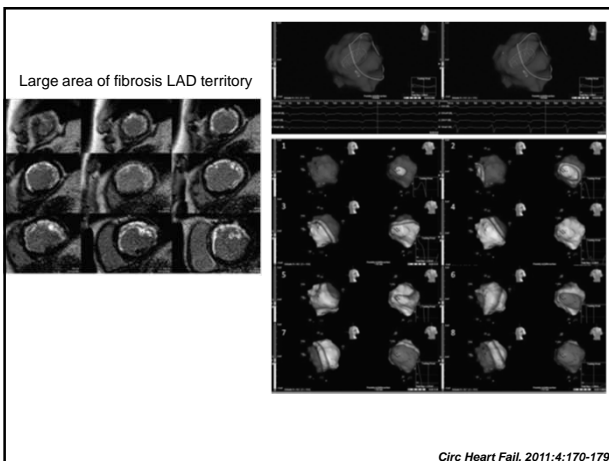
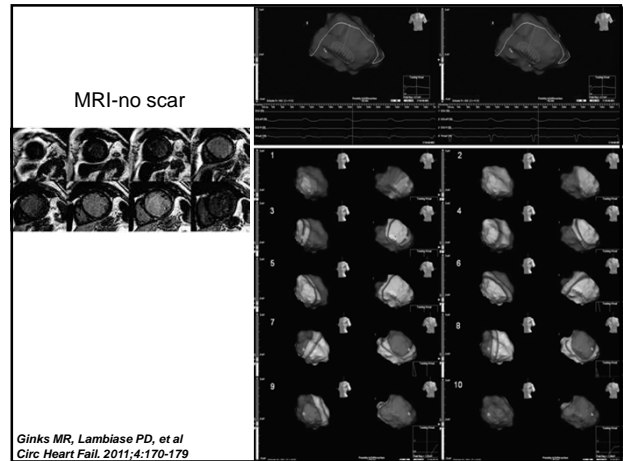
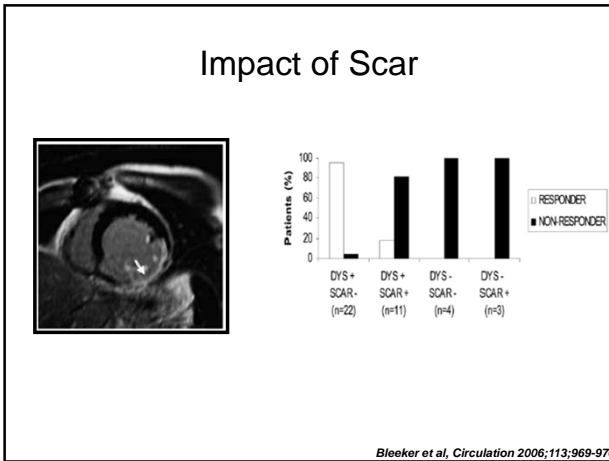
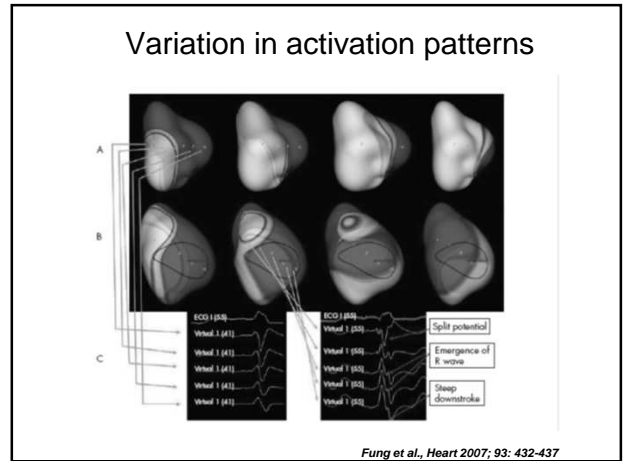
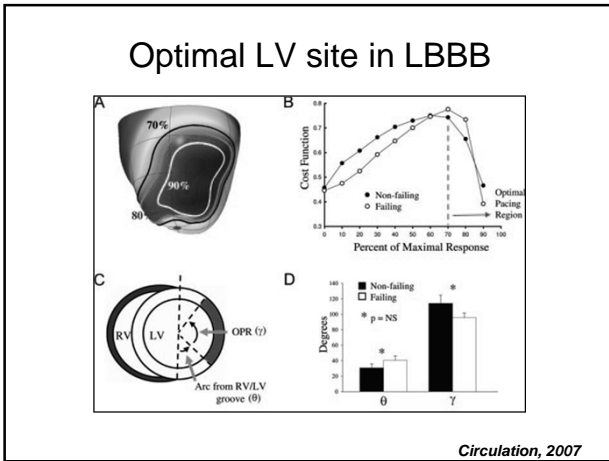
2289 patients with Heart Failure
NYHA Grade III or IV
35% reduction in all cause mortality

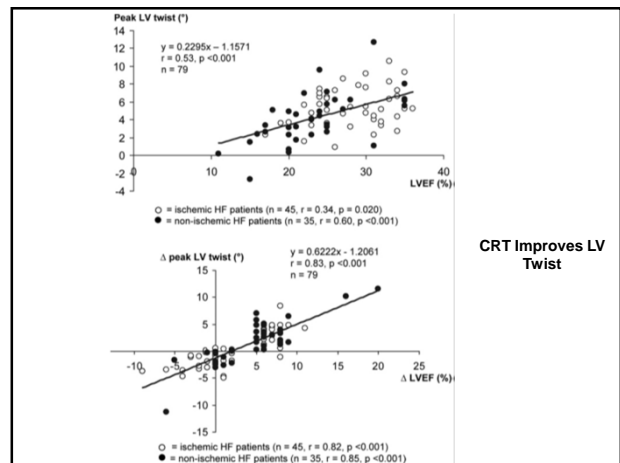
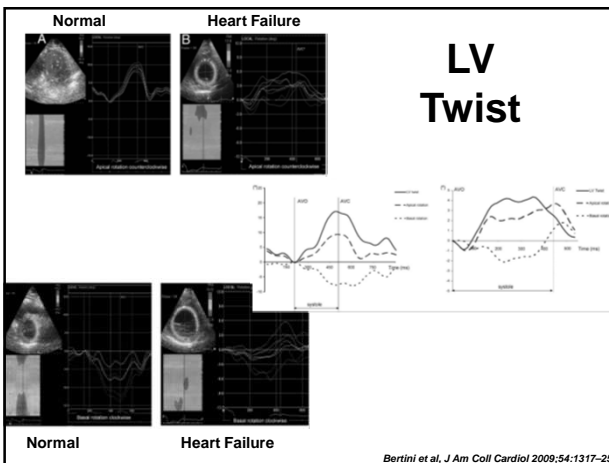
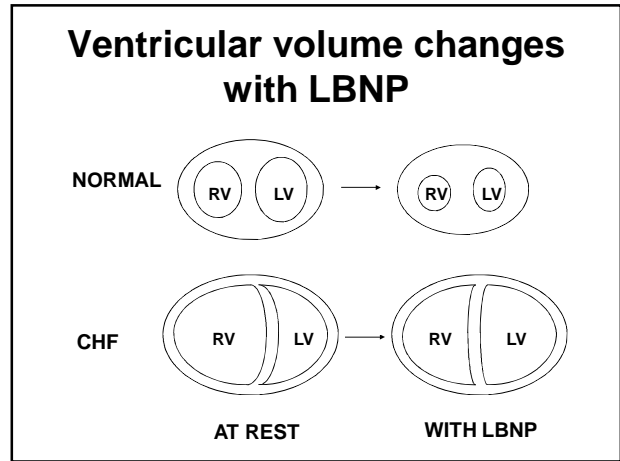
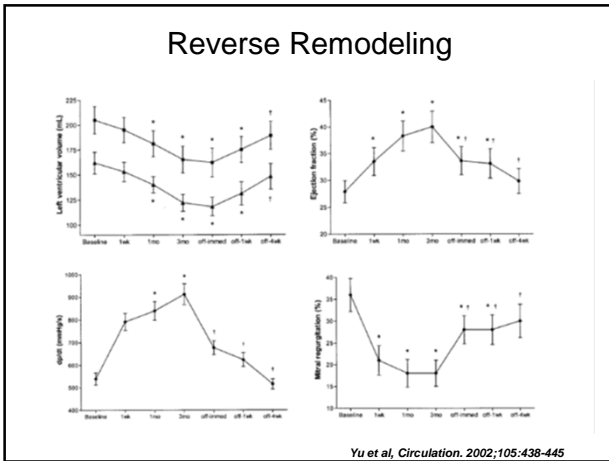
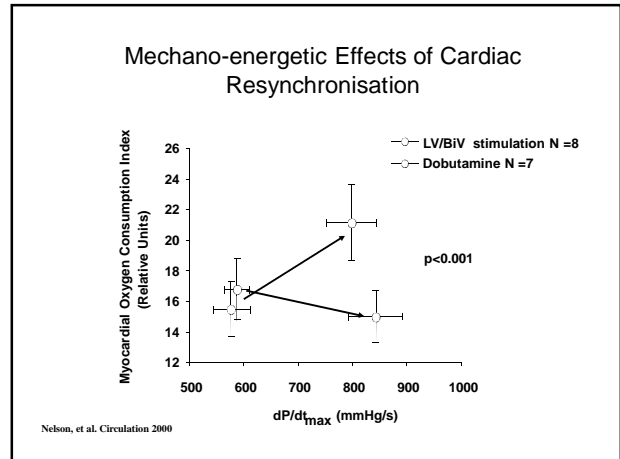
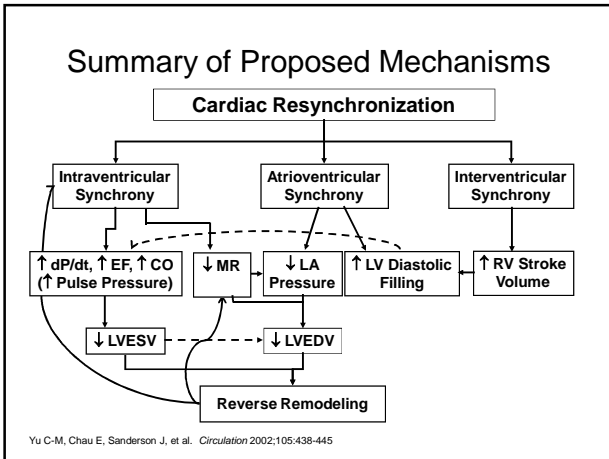
No. of Patients at Risk	
Placebo	1133 937 703 580 466 286 183 114
Carvedilol	1156 947 733 620 479 321 208 142

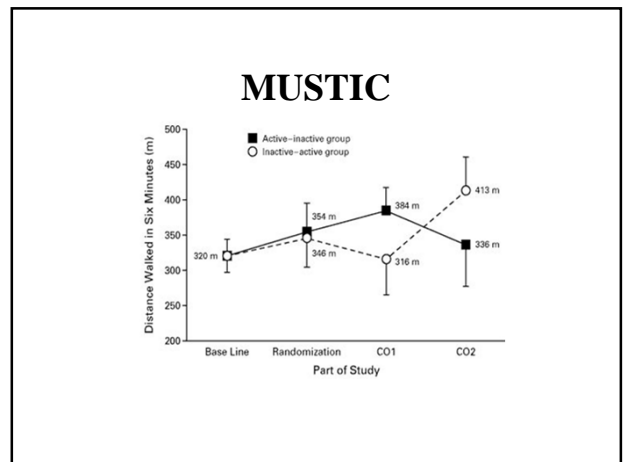
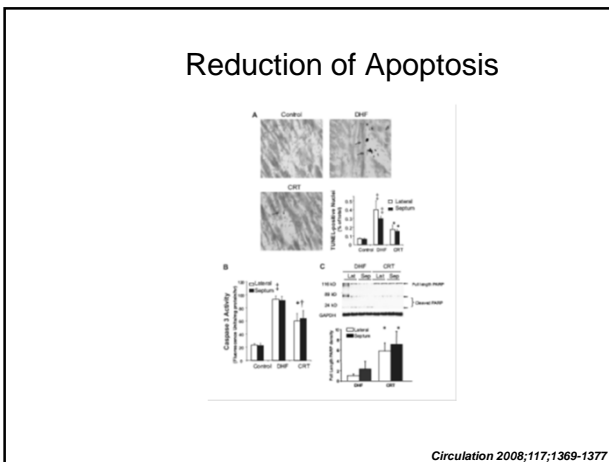
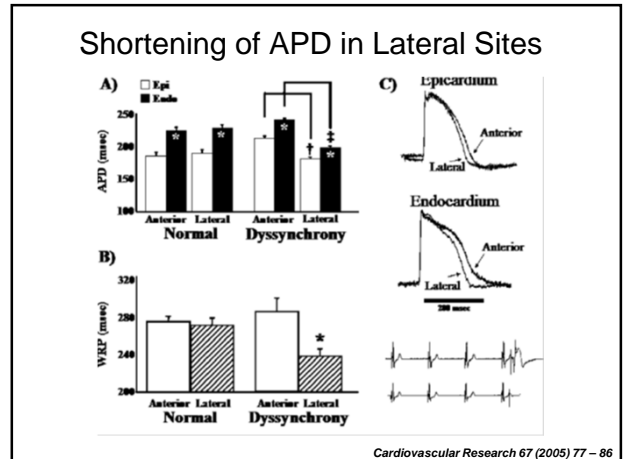
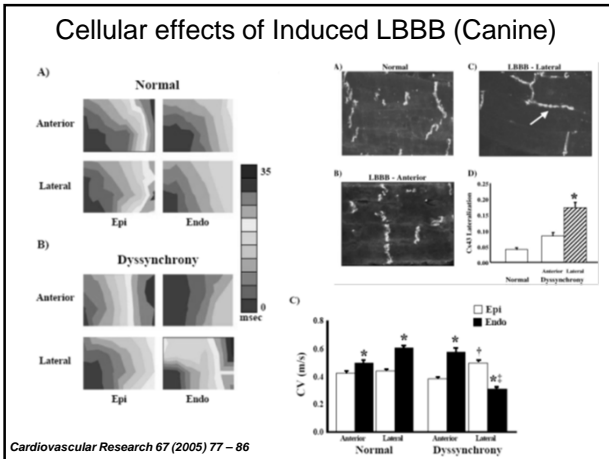
Packer M et al. N Engl J Med 2001;344:1651-1658



Gold 1st epicardial BV Annals thoracic Surgery







CRT Improves Quality of Life Score and NYHA Functional Class

	QoL	NYHA
PATH-CHF ¹ (n=41)	+	+
InSync (Europe) ² (n=103)	+	+
InSync ICD (Europe) ³ (n=84)	+	+
MUSTIC ⁴ (n=67)	+	
MIRACLE ⁵ (n=453)	+	+
MIRACLE ICD ⁶ (n=364)	+	+

+ Statistically significant improvement with CRT (p ≤ 0.05)
 ↔ Not statistically significant or No statistical analysis performed on data
 Blank Indicates test neither performed nor reported

¹ Auricchio A, Stellbrink C, Sack S., et al. *J Am Coll Cardiol* 2002;39:2026-2033
² Gras D, Leclercq C, Tang A, et al. *Eur J Heart Failure* 2002;4:311-320
³ Kuhlkamp V. *JACC* 2002;39:790-797
⁴ Linde C, Leclercq C, Rex S, et al. *J Am Coll Cardiol* 2002;40:111-118
⁵ Abraham W, Fisher W, Smith A, et al. *N Engl J Med*. 2002;346:1845-1853
⁶ Leon A. *NASPE Scientific Sessions – Late Breaking Clinical Trials*. May 2002; Medtronic Inc., data on file

CRT Improves Exercise Capacity

	6 Min Walk	Peak VO ₂	Exercise Time
PATH-CHF ¹ (n=41)	+	+	
InSync (Europe) ² (n=103)	+		
InSync ICD (Europe) ³ (n=84)	+		
MUSTIC ⁴ (n=67)	+	↔	
MIRACLE ⁵ (n=453)	+	+	+
MIRACLE ICD ⁶ (n=364)	↔	+	+

+ Statistically significant improvement with CRT (p ≤ 0.05)
 ↔ Not statistically significant or No statistical analysis performed on data
 Blank Indicates test neither performed nor reported

¹ Auricchio A, Stellbrink C, Sack S., et al. *J Am Coll Cardiol* 2002;39:2026-2033
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³ Kuhlkamp V. *JACC* 2002;39:790-797
⁴ Linde C, Leclercq C, Rex S, et al. *J Am Coll Cardiol* 2002;40:111-118
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⁶ Leon A. *NASPE Scientific Sessions – Late Breaking Clinical Trials*. May 2002; Medtronic Inc., data on file

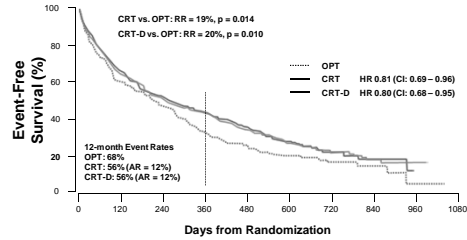
CRT Improves Cardiac Function/Structure

	LVEF	MR	Other
PATH-CHF ¹ (n=41)			+ LVEDP + LV dP/dt _{max}
InSync (Europe) ² (n=103)	+		+ Filling Time
InSync ICD (Europe) ³ (n=84)	+		+ Filling Time
MUSTIC ⁴ (n=67)	↔	↔	↔ LVEDD, LVESD ↔ Filling Time
MIRACLE ⁵ (n=453)	+		+ LVEDD, + LVEDV, LVESV
MIRACLE ICD ⁶ (n=362)	↔	+	+ LVEF, + LVEDV

+ Statistically significant improvement with CRT (p < 0.05)
 ↔ Not statistically significant or No statistical analysis performed on data
 Blank Indicates test neither performed nor reported

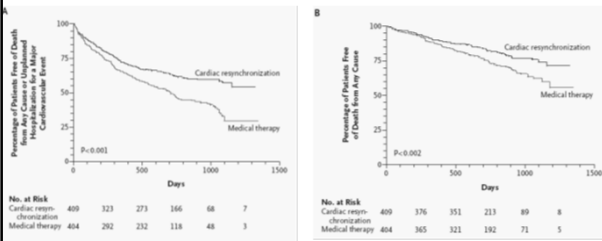
¹ Auricchio A, Stellbrink C, Sack S, et al. *J Am Coll Cardiol* 2002;39:2026-2033
² Gras D, Leclercq C, Tang A, et al. *Eur J Heart Failure* 2002;4:311-320
³ Kulkamp V. *JACC* 2002;39:790-797
⁴ Lunde C, Leclercq C, Rev S, et al. *J Am Coll Cardiol* 2002;40:111-118
⁵ Abraham W, Fisher W, Smith A, et al. *N Engl J Med* 2002;346:1845-1853
⁶ Young J. *ACC Scientific Sessions - Late Breaking Clinical Trials III*. March 2002; Medtronic Inc., data on file

COMPANION



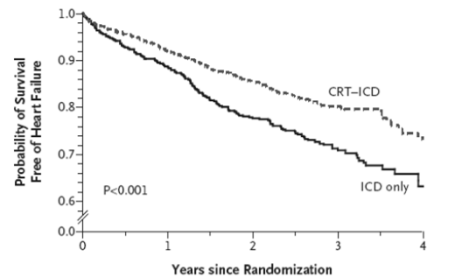
Bristow MR et al., *N Engl J Med*. 2004; 350:2140-215

Care-HF



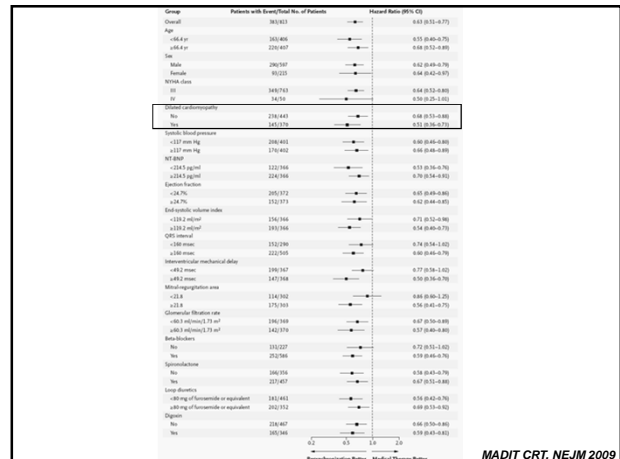
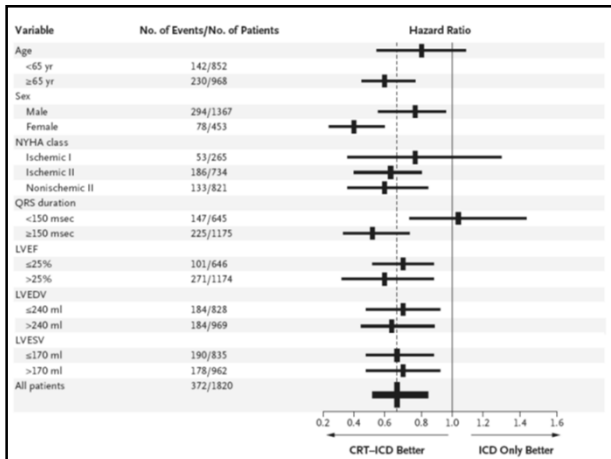
N Engl J Med 2005;352

Reverse Remodeling



No. at Risk (Probability of Survival)	0	1	2	3	4
ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT-ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

MADIT CRT, *NEJM* 2009



MADIT CRT, *NEJM* 2009

Cardiac Resynchronization

Randomized Trial of Cardiac Resynchronization in Mildly Symptomatic Heart Failure Patients and in Asymptomatic Patients With Left Ventricular Dysfunction and Previous Heart Failure Symptoms

Cecilia Linde, MD, PhD,* William T. Abraham, MD, FACC,† Michael R. Gold, MD, PhD,‡§
 Martin St. John Sutton, MD,§ Stefano Ghio, MD,¶ Claude Dubert, MD,|| on behalf of the REVERSE
 (Resynchronization with Ventricular Remodeling in Systolic left VEntricular dysfunction) Study Group
 Stockholm, Sweden; Columbus, Ohio; Charleston, South Carolina; Philadelphia, Pennsylvania;
 Paris, Italy and Rennes, France

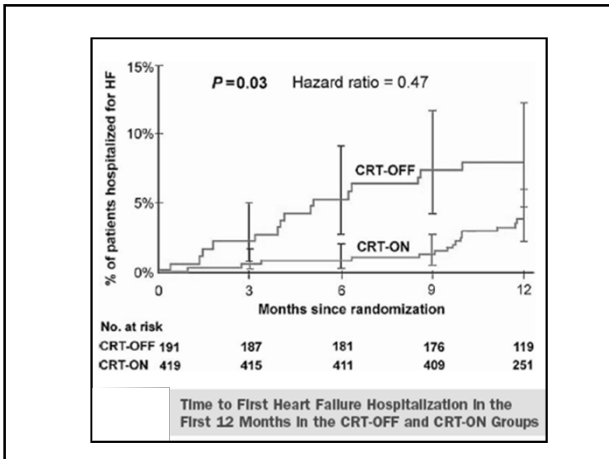
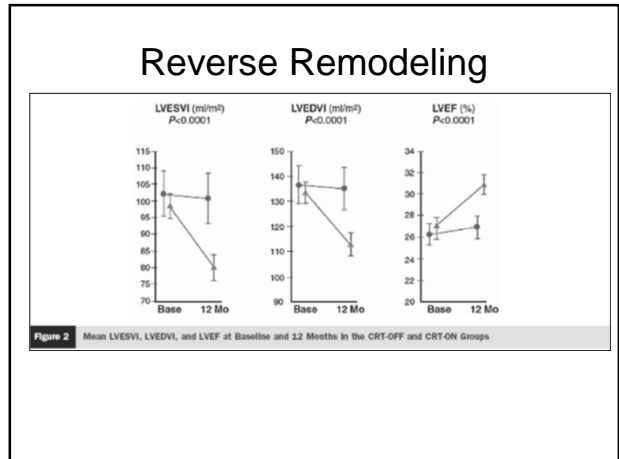
Objectives We sought to determine the effects of cardiac resynchronization therapy (CRT) in New York Heart Association (NYHA) functional class II heart failure (HF) and NYHA functional class I (American College of Cardiology/American Heart Association stage C) patients with previous HF symptoms.

Background Cardiac resynchronization therapy improves left ventricular (LV) structure and function and clinical outcomes in NYHA functional class II and IV HF with prolonged QRS.

Methods Six hundred ten patients with NYHA functional class I or II heart failure with a QRS >120 ms and a LV ejection fraction <40% received a CRT device (n = 500) or were randomly assigned to active CRT (CRT-ON; n = 438) or control (CRT-OFF; n = 191) for 12 months. The primary end point was the HF clinical composite response, which scores patients as improved, unchanged, or worsened. The prospectively powered secondary end point was LV end-systolic volume index. Hospitalization for worsening HF was evaluated in a prospective secondary analysis of health care use.

Results The HF clinical composite response end point, which compared only the percent worsened, indicated 35% worsened in CRT-ON compared with 25% in CRT-OFF (p = 0.10). Patients assigned to CRT-ON experienced a greater improvement in LV end-systolic volume index (-18.4 ± 29.5 mL/m² vs. -1.3 ± 23.4 mL/m²; p < 0.0002) and other measures of LV remodeling. Time-to-first HF hospitalization was significantly reduced in CRT-ON (hazard ratio: 0.47, p = 0.03).

Conclusions The REVERSE (Resynchronization with Ventricular Remodeling in Systolic left VEntricular dysfunction) trial demonstrates that CRT, in combination with optimal medical therapy (i.e., defibrillator), reduces the risk for heart failure hospitalization and improves ventricular structure and function in NYHA functional class II and NYHA functional class I (American College of Cardiology/American Heart Association stage C) patients with previous HF symptoms. (Resynchronization with Ventricular Remodeling in Systolic Left VEntricular Dysfunction [REVERSE]; NCT00271554. J Am Coll Cardiol 2006; 52:834-43) © 2006 by the American College of Cardiology Foundation



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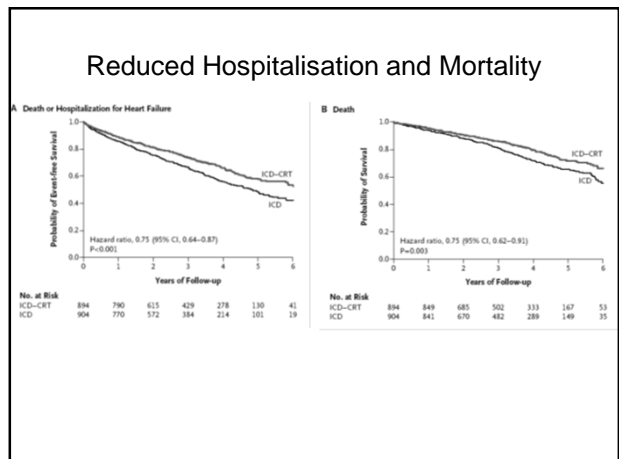
Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure

Anthony S.L. Tang, M.D., George A. Wells, Ph.D., Mario Talajic, M.D., Malcolm O. Arnold, M.D., Robert Sheldon, M.D., Stuart Connolly, M.D., Stefan H. Hohnloser, M.D., Graham Nichol, M.D., David H. Birnie, M.D., John L. Sapp, M.D., Raymond Yee, M.D., Jeffrey S. Healey, M.D., and Jean L. Rouleau, M.D., for the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) Investigators

Class II-III Heart Failure

Table 2. Risk of Death or Hospitalization for Heart Failure among All Patients and According to New York Heart Association (NYHA) Category.

Outcome	ICD (N=904)	ICD-CRT (N=894)	Hazard Ratio (95% CI)	P Value
All patients				
Primary outcome: death or hospitalization for heart failure	364 (40.3)	297 (33.2)	0.75 (0.64-0.87)	<0.001
Secondary outcomes				
Death from any cause	236 (26.1)	186 (20.8)	0.75 (0.62-0.91)	0.003
Death from cardiovascular cause	162 (17.9)	130 (14.5)	0.76 (0.60-0.96)	0.02
Hospitalization for heart failure	236 (26.1)	174 (19.5)	0.68 (0.56-0.83)	<0.001
Patients in NYHA class II				
No. of patients	730	708		
Primary outcome: death or hospitalization for heart failure	253 (34.7)	193 (27.3)	0.73 (0.61-0.88)	0.001
Secondary outcomes				
Death from any cause	154 (21.1)	110 (15.5)	0.71 (0.56-0.91)	0.006
Death from cardiovascular cause	100 (13.7)	74 (10.5)	0.73 (0.54-0.99)	0.04
Hospitalization for heart failure	159 (21.8)	115 (16.2)	0.70 (0.55-0.89)	0.003
Patients in NYHA class III				
No. of patients	174	186		
Primary outcome: death or hospitalization for heart failure	111 (63.8)	104 (55.9)	0.76 (0.58-0.99)	0.04
Secondary outcomes				
Death from any cause	82 (47.1)	76 (40.9)	0.79 (0.58-1.08)	0.14
Death from cardiovascular cause	62 (35.6)	56 (30.1)	0.77 (0.54-1.10)	0.15
Hospitalization for heart failure	77 (44.3)	59 (31.7)	0.63 (0.45-0.88)	0.006



Moss Meta-anlaysis-JACC

Conclusions

- CRT-D is now an established therapy for heart failure with broad QRS which reduces mortality
- Exerts significant positive effects on LV remodelling both mechanical and electrical
- Translates into reduced hospitalisations not only in NYHA III-IV but mild heart failure
- Major implications to modify and slow disease progression and reduce mortality

Challenges:

- (i) Identification mild HF patients most likely to benefit
- (ii) Timing and cost-efficacy of intervention

