Update of Clinical Study and Unresolved Issues in Cardiac Resynchronization Therapy

전북의대 이경석

Relationship of the Implantable Cardioverter Defibrillator and Chronic Resynchronization Therapy: The Perfect Marriage?

David S. Cannom, M.D., and Morton Mower, M.D.

Good Samaritan Hospital Los Angeles, Los Angeles, California *ANE Suppl 2005;10:24*

Table 1. Mirowski/Mower Legacy of Pivotal Therapies

	ICD	CRT
Concept	1970	Mid 1970s
Patent	1971	1990
First implant	1981	1991
FDA/CMS approval	1984	2004
Pivotal trials	MADIT I & II	COMPANION
	SCD-HeFT	CARE-HF
	AVID	
	CIDS	

CRT Studies **before** COMPANION/CARE-HF

- Short-term studies and "On-therapy" analysis.
- Changes in Functional status:
  * Positive change for some, but not all, measures
  * Inconsistent changes within and across studies.
- All-cause mortality and Total hospitalization:
  * No significant change – MIRACLE, VENTAK CHF/CONTAK CD, or InSync ICD.
  * All studies Underpowered (small sample sizes).

COMPANION	CARE-HF
Inclusion	*Inclusion*
Class III – IV CHF	Class III – IV CHF
EF ≤ 35% (M = 21%)	EF ≤ 35% (M = 25%)
QRS ≥ 120 ms, NSR	QRS ≥ 120 ms, NSR
Ischemic (56%)	Ischemic (38%)
No. Pts. = **1520**	No. Pts. = **813**
Randomization	*Randomization*
OPT vs CRT vs **CRT-D** **(1:2:2)**	OPT vs CRT **(1:1)**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Michael R. Bristow, M.D., Leslie A. Saxon, M.D., John Boehmer, M.D., Steven Krueger, M.D., David A. Kass, M.D., Teresa De Marco, M.D., Peter Carson, M.D., Lorenzo DiCarlo, M.D., David DeMets, Ph.D., Bill G. White, Ph.D., Dale W. DeVries, B.A., and Arthur M. Feldman, M.D., Ph.D., for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators*

NEJM 2004;350:2140

COMPANION: Endpoints

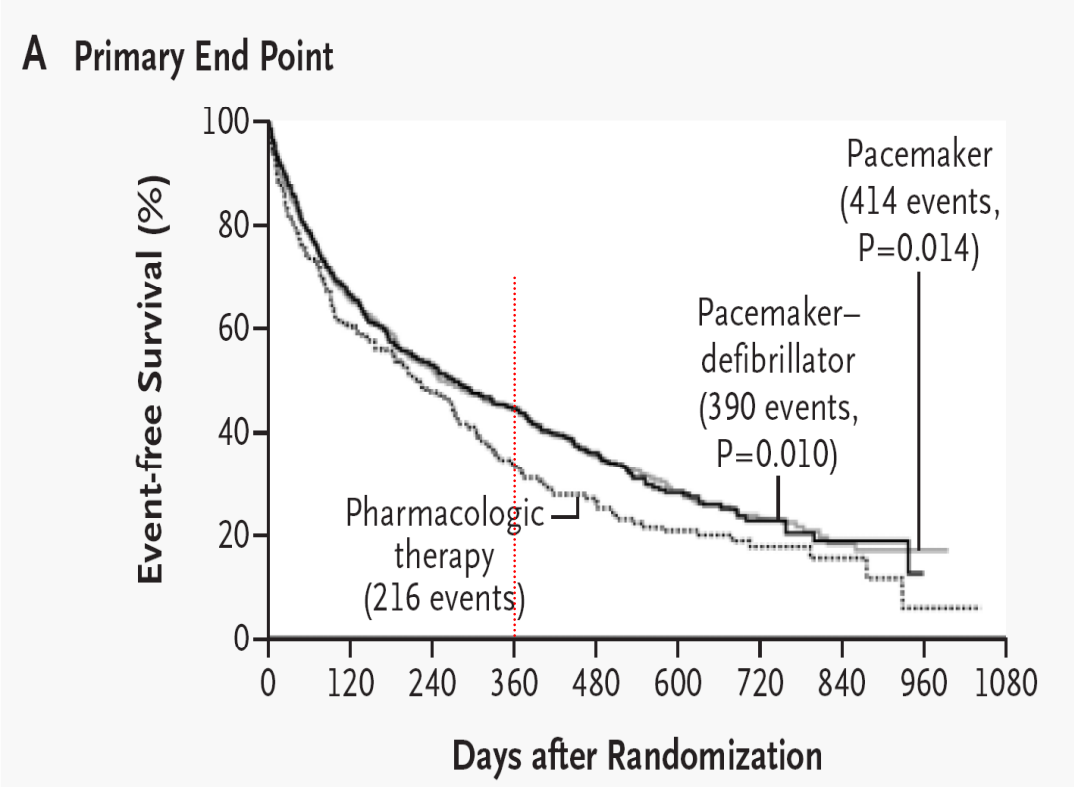
1. Primary
   * Composite of Death or Hospitalization (both any-cause)
     - *Definition of hospitalization: all-cause except elective admission for CRT*

2. Secondary
   * All-cause mortality, Cardiac morbidity, Exercise performance (Sub-Study: J Cardiac Fail 2008;14:9)

3. Tertiary
   * Submaximal exercise, QoL…

COMPANION: *Total of 1020 primary endpoints were analyzed*

*** Composite of Death or Any Hospitalization**



12-month event rate :

OPT 68 %

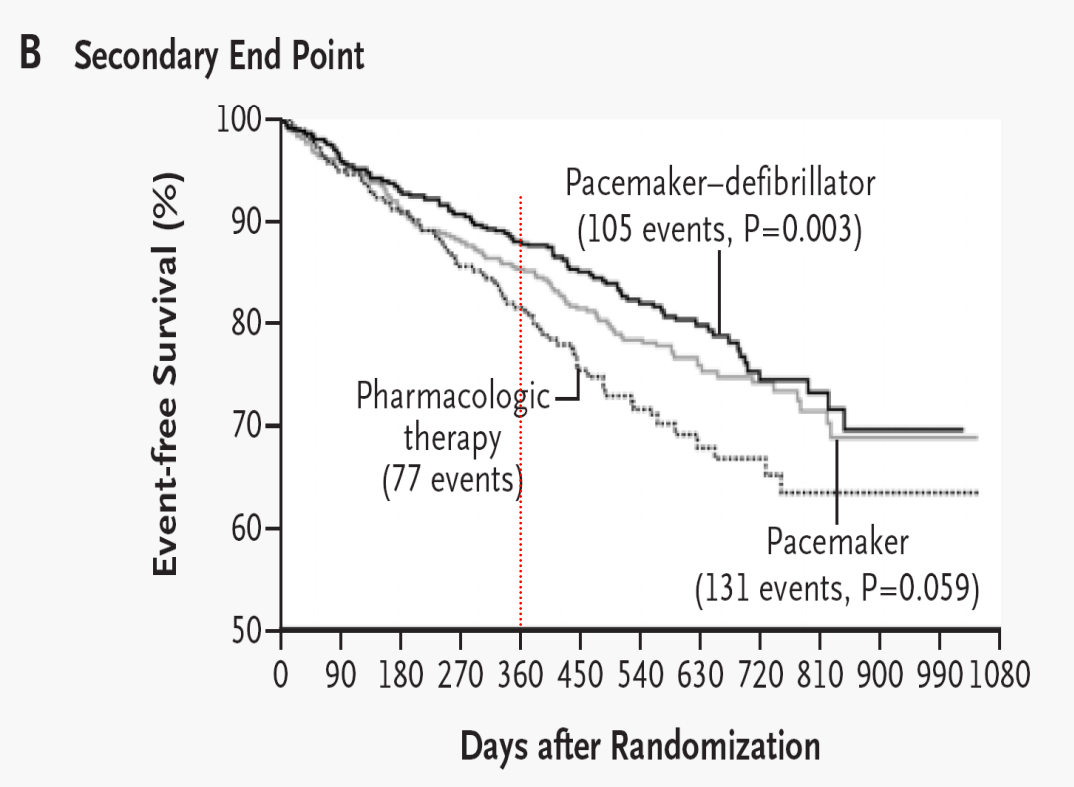
CRT 56 %

CRT-D 56%

→ **Reductions: ~ 20 %**

COMPANION: *Secondary Endpoint*

*** All-Cause Mortality**



12 mo Event Rate :

OPT 19 %

CRT 15 %

CRT-D 12 %

→ Reductions:

CRT = 24% (P=.06)

CRT-D = **36%** (P=.004)

Benefit of CRT on mortality takes time (reverse remodeling), ICD benefit is immediate.

Mode of Death in Advanced Heart Failure

The Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) Trial *JACC 2005;46:2329*

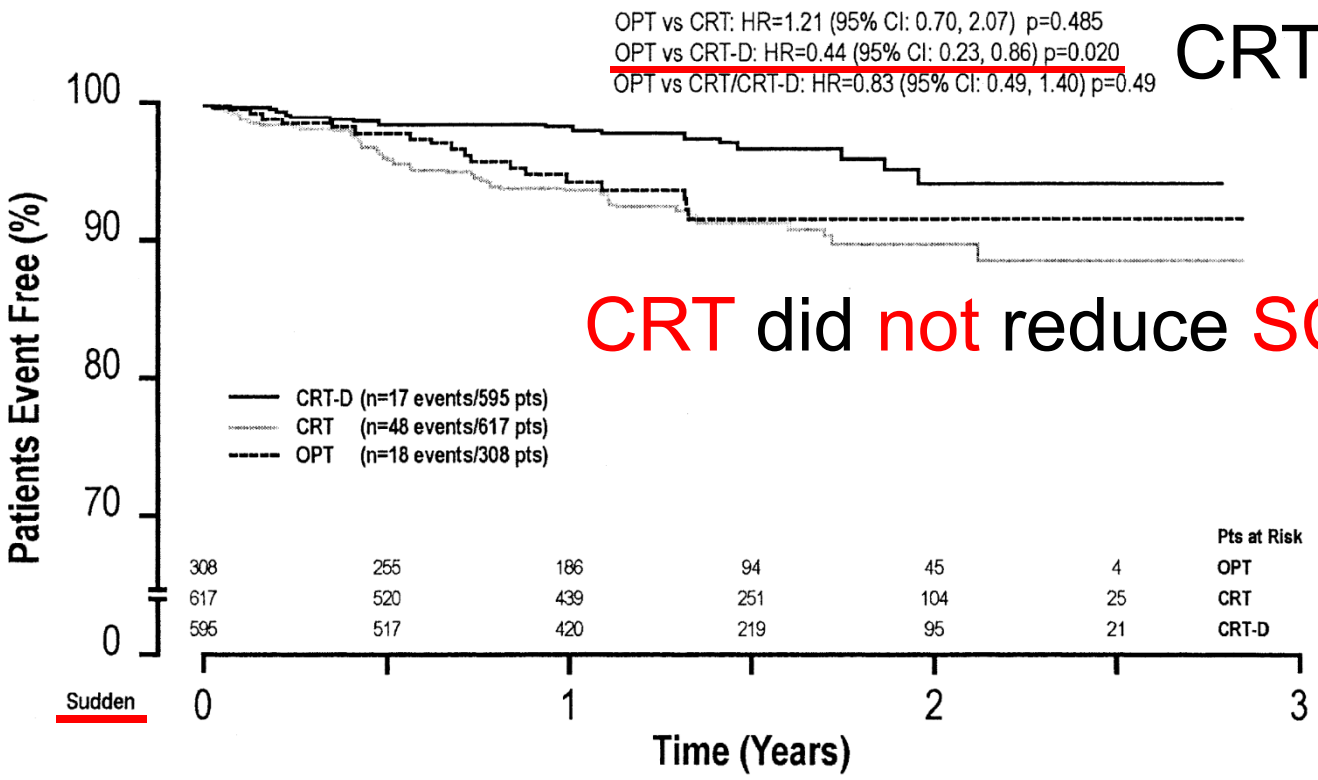


Figure 3. Kaplan-Meier estimate of the time to first sudden cardiac death. Abbreviation as in Figure 1.

Predictors of Sudden Cardiac Death and Appropriate Shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial *Circulation 2006;114:2766*

Mean 15.7 mo F/U
83 SD / 1519 pts

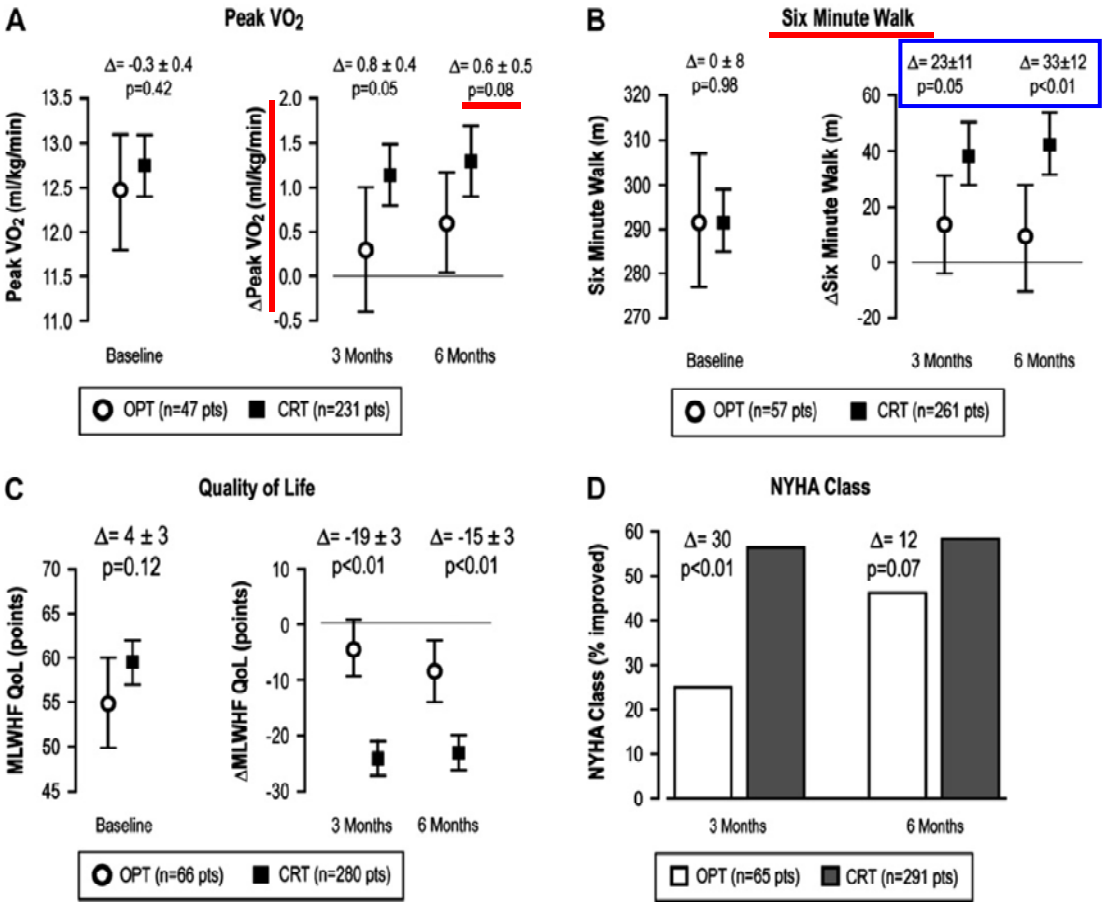
OPT 5.8%
CRT 7.8%
CRT-D **2.9%**

TABLE 2. Risk of Sudden Cardiac Death

		Sudden Cardiac Death (n=83/1519)		
	Variable	Hazard Ratio	*P* Value	95% CI
	CRT-D	0.47	0.02	(0.24 to 0.91)
	CRT	1.21	0.48	(0.71 to 2.09)
Favorable	LVEF >20%	0.55	0.01	(0.35 to 0.87)
Favorable	QRS >160 ms	0.63	0.05	(0.40 to 0.997)
Favorable	Female gender	0.47	<0.01	(0.27 to 0.82)
Unfavorable	NYHA class IV	2.62	<0.01	(1.61 to 4.26)
Unfavorable	Renal dysfunction	1.69	0.03	(1.06 to 2.69)

Impact of Cardiac Resynchronization Therapy on **Exercise Performance**, Functional Capacity, and Quality of Life in Systolic Heart Failure With QRS Prolongation: **COMPANION** Trial Sub-Study J Cardiac Fail 2008;14:9

1°End point: Δ peak VO_2



1°End point

Data missing : 31% at 6mo

→ No difference between Tx groups.

Within Tx groups

CRT ↑($P < .05$)

Δ: 1.13ml/kg/min at 3mo,
1.26 at 6 mo

OPT: no significant ↑

Predictor of Clinical Outcome

peak VO_2 < 12.5ml/kg/min

→ mortality (↑3x) in CRT cohort

COMPANION:

Summary of Major Outcomes

- Reduction in the Combined Endpoints of Death + all cause Hospitalization was due to CRT
- Therapy with an ICD in addition to CRT substantially increased the mortality reduction, attributable to reduction in SCD (HR 0.64)
- Follow up only 12 months

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

John G.F. Cleland, M.D., Jean-Claude Daubert, M.D.,
Erland Erdmann, M.D., Nick Freemantle, Ph.D., Daniel Gras, M.D.,
Lukas Kappenberger, M.D., and Luigi Tavazzi, M.D.,
for the Cardiac Resynchronization — Heart Failure (CARE-HF) Study Investigators*

NEJM 2005;352:1539

CARE-HF

1. Primary endpoint

: composite of Death from any cause or Hospitalization for a major cardiovascular event.

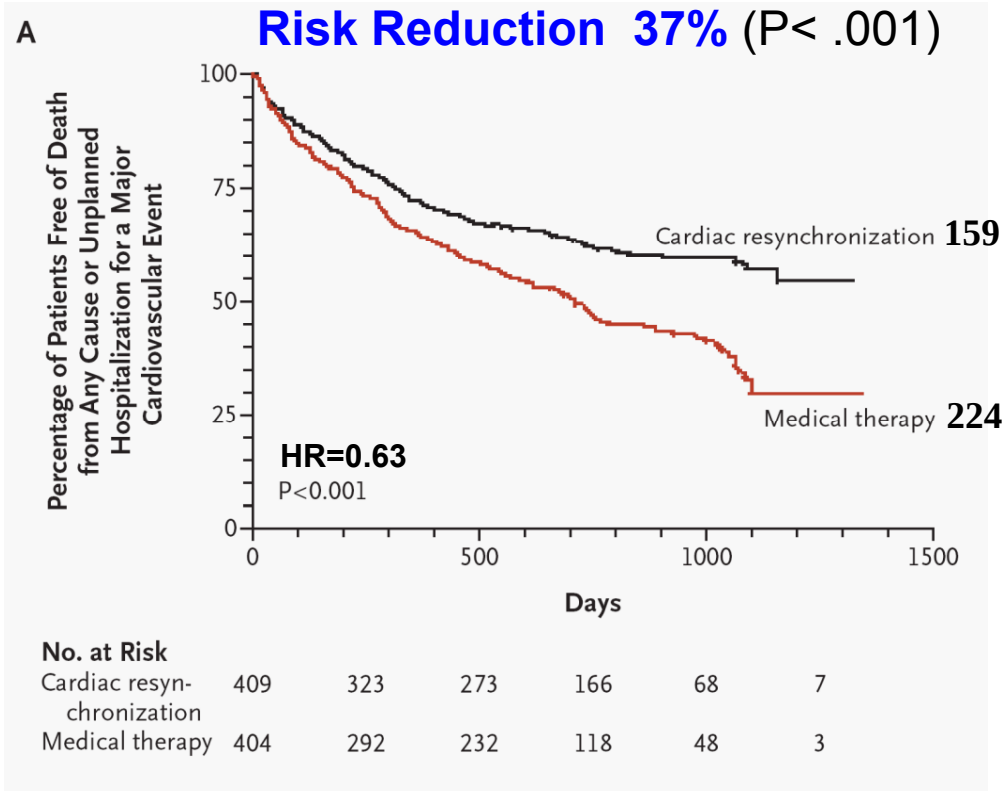
2. Secondary endpoint

: Death from any cause classified according to endpoint.

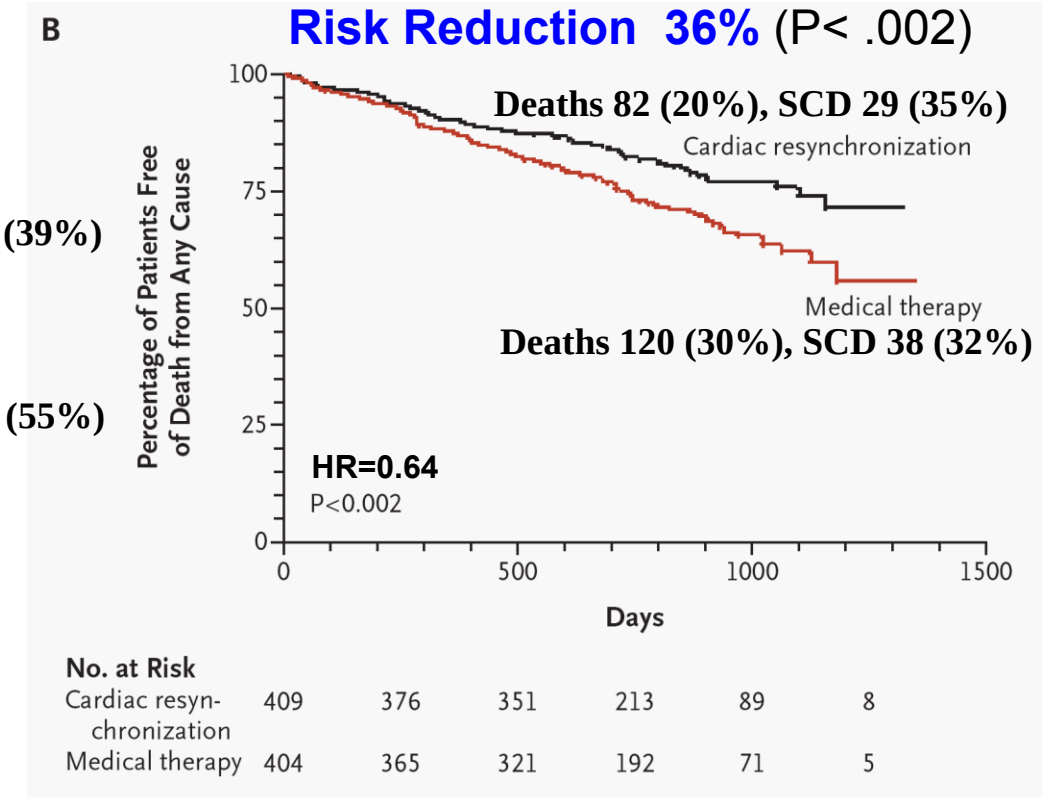
Kaplan-Meier Estimates of the Time to the Primary End Point and the Principal Secondary Outcome

29.4 months

1° End point



2° End point



Quality of Life Data from CARE-HF Study Outcomes in Analyses Stratified According to NYHA Class

	Medical Therapy Alone (N=404)	Medical Therapy plus Cardiac Resynchronization (N=409)	Difference in Means (95% CI)‡	P Value
	value at 90 days			
Continuous outcome				
NYHA class	2.7±0.9	2.1±1.0	0.6 (0.4 to 0.7)	<0.001
Minnesota Living with Heart Failure score§	40±22	31±22	−10 (−8 to −12)	<0.001
EuroQoL EQ-5D score¶	0.63±0.29	0.70±0.28	0.08 (0.04 to 0.12)	<0.001

Pt' number *at 18 months*

NYHA class	OPT		CRT
I	39	<	105
II	112	<	150
III ~ IV	152	>	80

Conclusion of CARE-HF

- CRT alone reduces total mortality by 36% (*HR 0.64, P<.002*)
- Effect continued over 18 months
- BNP level decreased at 3 mo, further↓ at 18 months (1,122 pg/ml)
- However a significant number of SCDs (35%) occurred in the CRT arm some of which could be prevented

COMPANION somewhat higher risk population than **CARE-HF**

	CARE-HF (n=813)			COMPANION (n=1520)		
	OPT		CRT-P	OPT		CRT-P
Age (yrs)	66	**66.5**	67	68	**67.5**	67
Male (%)	73	**73.5**	74	69	**68**	67
NYHA IV (%)	7	**6.5**	6	18	**15.5**	13
QRS (ms)	160	**160**	160	158	**159**	160
EF (%)	25	**25**	25	22	**21**	20
CAD (%)	35	**38**	41	59	**56.5**	54

1-year Control Group Mortality:

COMPANION **19 %** > CARE-HF **12.6 %**

Mode of Death in Advanced Heart Failure The Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) Trial JACC 2005;46:2329

Strikingly Similar

Table 1. Mode of Death Overall, and Within Each Treatment Group

Cause of Death	OPT n (%*) [%†]	CRT n (%*) [%†]	CRT-D n (%*) [%†]	CARE-HF n (%) OPT	CARE-HF n (%) CRT
Number of patients	308	617	595		
Cardiac	54 (18.8) [75.3]	109 (17.1) [83.2]	76 (12.8) [72.4]		
SCD	18 (5.8) [23.4]	48 (7.8) [36.6]	17 (2.9) [16.2]	38 (32)	29 (35)
Pump failure	34 (11.0) [44.2]	53 (8.6) [40.5]	52 (8.7) [49.5]	56 (47)	33 (40)
Ischemic	4 (1.3) [5.2]	2 (0.3) [1.5]	4 (0.7) [3.8]		
Cardiac procedure	2 (0.6) [2.6]	6 (1.0) [4.6]	2 (0.3) [1.9]		
Others	0 (0) [0]	0 (0) [0]	1 (0.2) [1.0]		
Vascular	0 (0) [0]	5 (0.8) [3.8]	3 (0.5) [2.8]		
Non-cardiac	11 (3.6) [14.3]	14 (2.3) [10.7]	21 (3.5) [20.0]		
Unknown	8 (2.6) [10.4]	3 (0.5) [2.3]	5 (0.8) [4.8]		
Total	77 (25.0)	131 (21.2)	105 (17.6)		

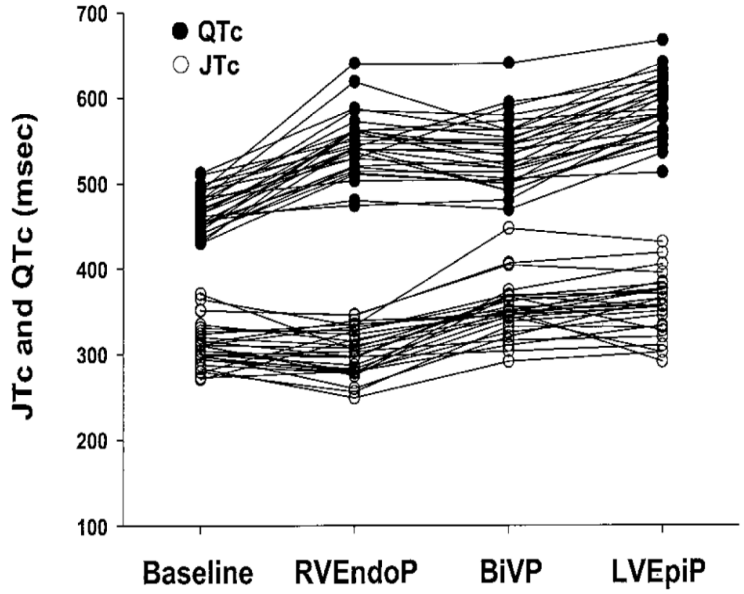
*% of deaths by randomized patients within each group. †% of deaths within each treatment group.

Early and Late Hemodynamic and Electrophysiologic Effects of CRT

- Proarrhythmia & Long Term Sustained Benefit

Effect of Epicardial or Biventricular Pacing to Prolong QT Interval and Increase Transmural Dispersion of Repolarization. *Does Resynchronization Therapy Pose a Risk for Patients Predisposed to Long QT or Torsade de Pointes?* *Circulation 2003;107:740*

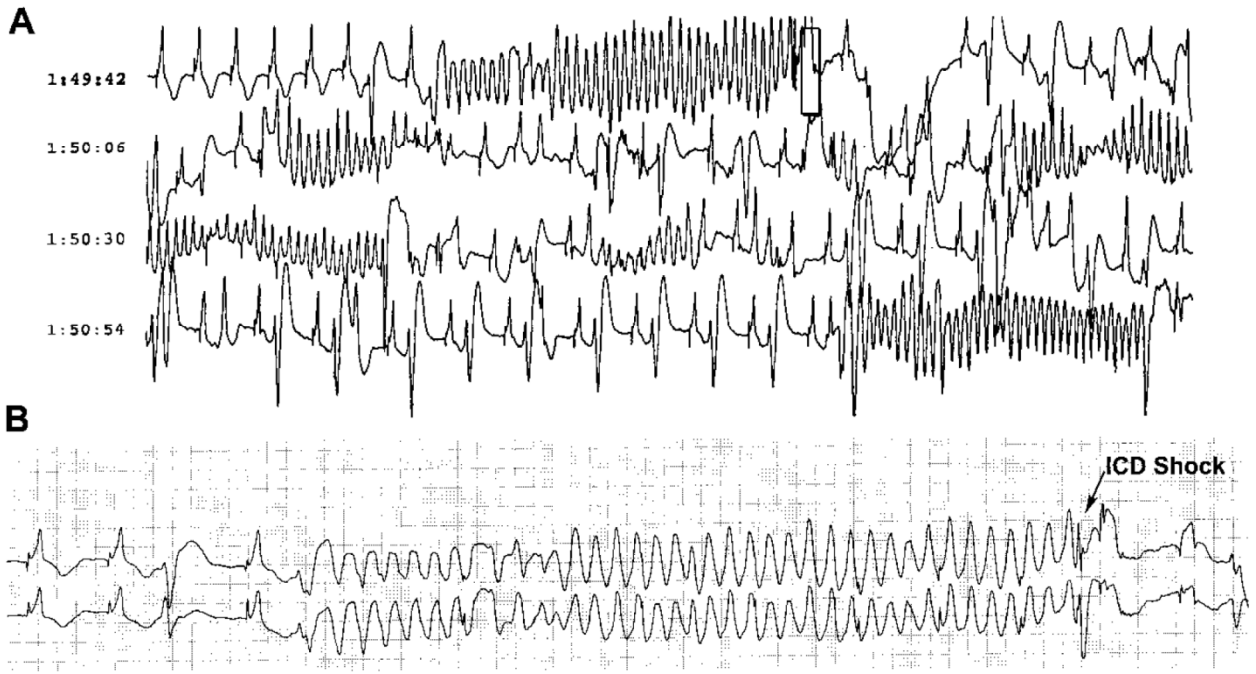
Comparison of the QT interval and JT interval among baseline rhythm, RV Endocardial, biventricular, and LV epicardial pacing in 29 pts.



→ Early Effect

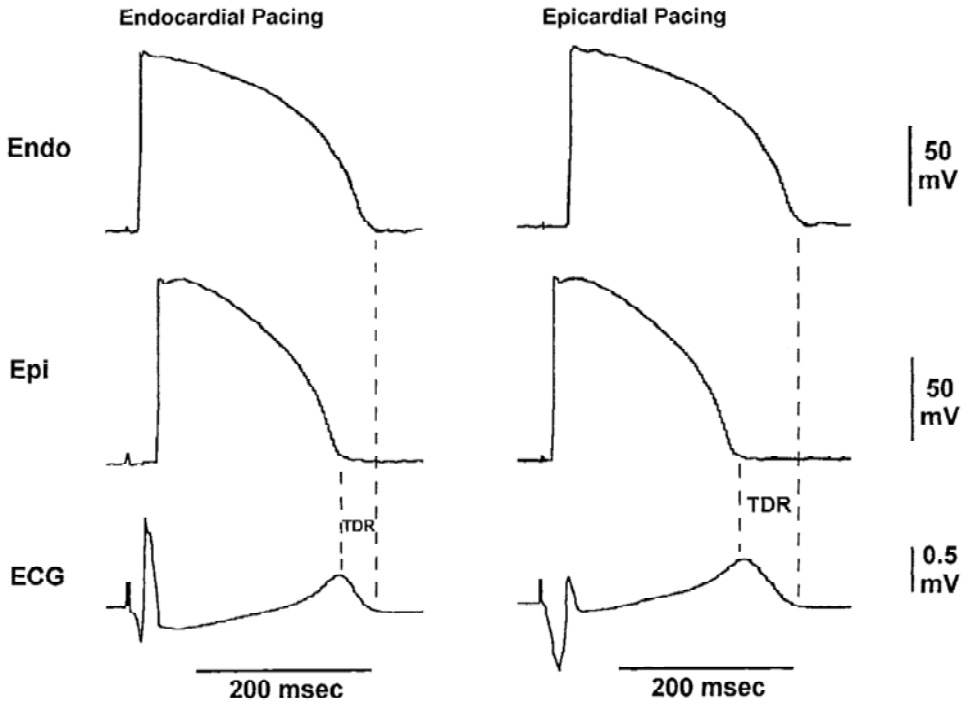
Effect of Epicardial or Biventricular Pacing to Prolong QT Interval and Increase Transmural Dispersion of Repolarization. *Does Resynchronization Therapy Pose a Risk for Patients Predisposed to Long QT or Torsade de Pointes?* *Circulation 2003;107:740*

Incessant R-on-T VPCs and TDP post BiV



Effect of Epicardial or Biventricular Pacing to Prolong QT Interval and Increase Transmural Dispersion of Repolarization *Cricculation 2003;107:740*

Pacing site-dependent Changes in QT Interval and TDR in an Arterially-perfused Rabbit LV Wedge Preparation



Early Effect

Impact of Upgrade to Cardiac Resynchronization Therapy on Ventricular Arrhythmia Frequency in Patients With Implantable Cardioverter-defibrillators

JACC 2005;46:2258

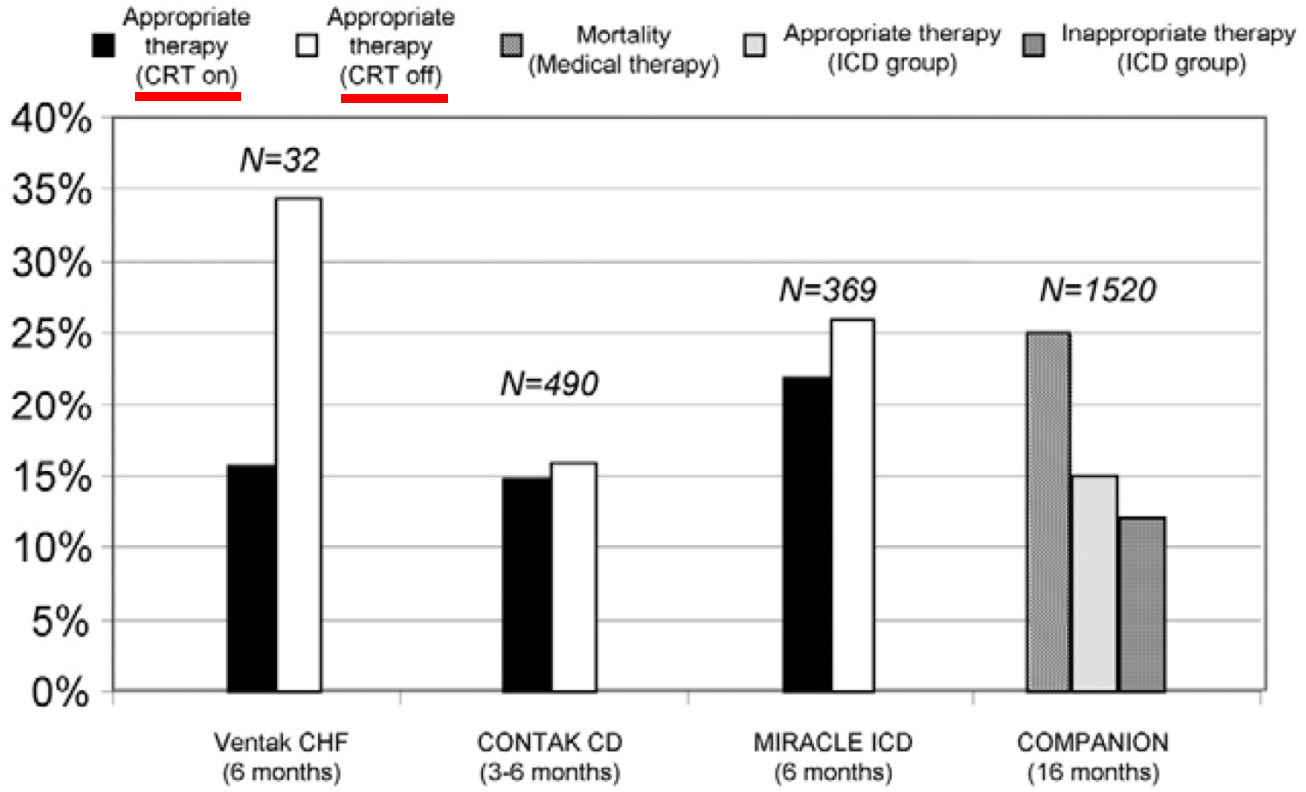
- Positive Effect of CRT
  - ↓ Wall stress
  - ↓ Ischemia → Late Effects
  - ↑ Cardiac Output
- Negative Effect of CRT
  - Altered direction & duration of LV repolarization
- ? Effect
  - → Cancel each other

Rates of therapies in major CRT-D trials

Frequency and Causes of ICD Therapies: **Is Device Therapy Proarrhythmic?**

Joseph J. Germano, DO, Matthew Reynolds, MD, MSc, Vidal Essebag, MD, PhD, and Mark E. Josephson, MD*,†

AJC 2006;97:1255



BiV pacing: Is It Proarrhythmic?

- Clinical Reports of Early Incessant VT after BiVP (JCE 2005;16:655, Heart Rhythm 2005;2:951)
- Ventak CHF : Decrease in ATP for VT after BiVP (JACC 2000;36:824)
- Compare BiVP with LVepi. QTc dispersion ↑ during LVepi,

  Unaffected during BiVP (JCE 2006;17:151)
- **Large scale clinical BiVP trials do Not report Proarrhythmia**
- Continued Reports of Early Incessant VT after BiVP (JCE 2008 Mar 20 Epub)

→*In **Recently Underwent** CRT, **Small** in Number though,*

***Proarrhythmic Potential** of LV Epicardial Pacing **Should be Considered**.*

Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the Cardiac REsynchronization-Heart Failure (CARE-HF) trial extension phase] *EHJ 2006;27:1928*

Mean F/U: 36.4 mo

1° outcome : All cause mortality 40%↓

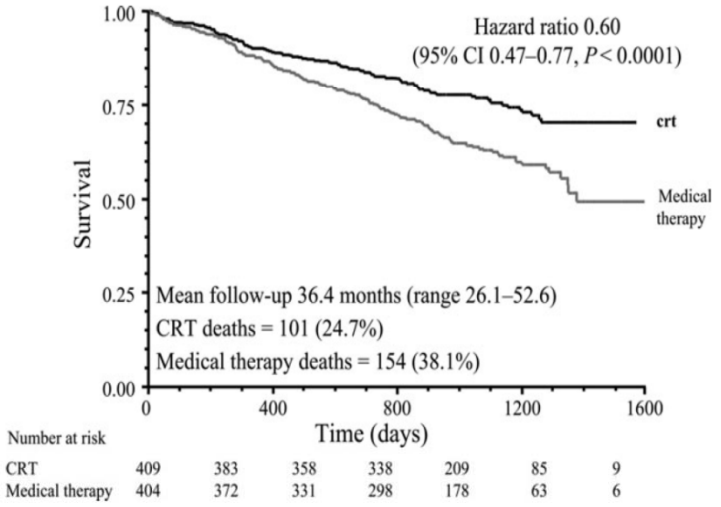


Figure 1 The Kaplan–Meier estimates of the time to all-cause mortality.

2° outcome : Mode of Death

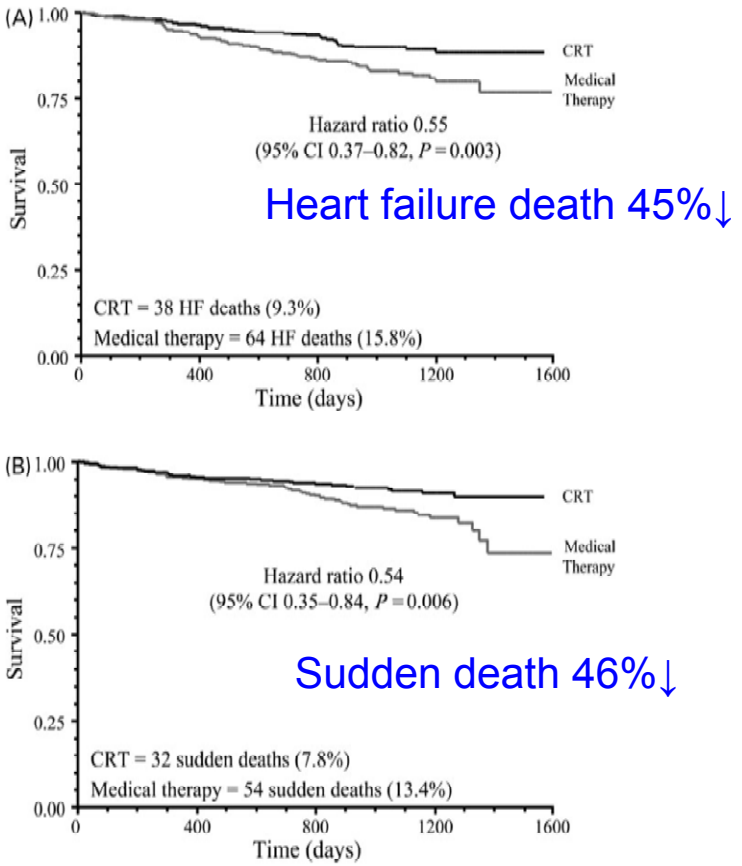


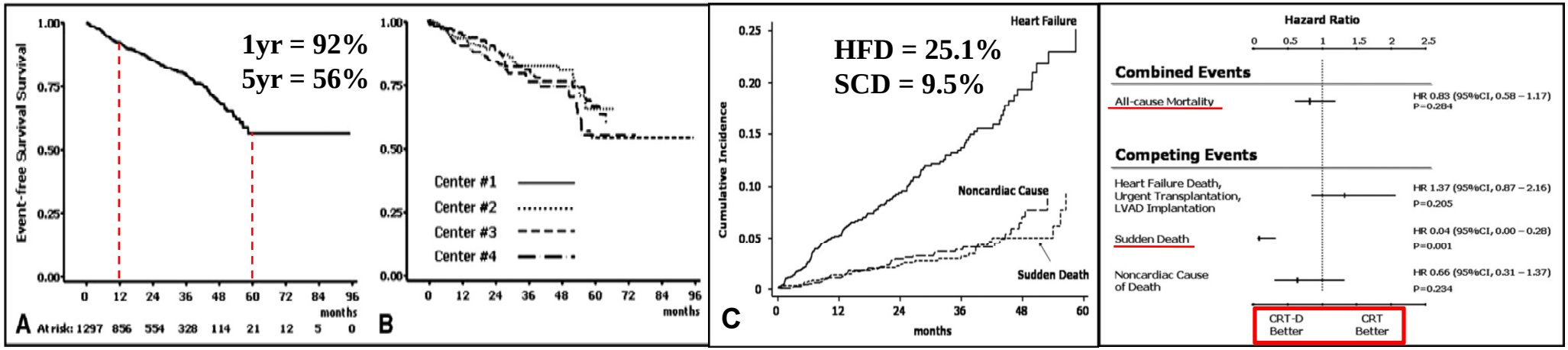
Figure 2 The Kaplan–Meier estimates of the time to death from worsening heart failure (*A*) or sudden death (*B*).

Long-Term Survival of Patients With Heart Failure and Ventricular Conduction Delay Treated With Cardiac Resynchronization Therapy

- **Multicenter** Longitudinal **Observational Study** (**MILOS**) - AJC2007;99:232

4 European Centers, Enroll 1,303 for **8 years** → Analyze 1060 (82%)

NYHA II,III,IV (5, 80, 15%), **CRT : CRT-D** = 454:606, 1° End point: Death+TPL+LVAD



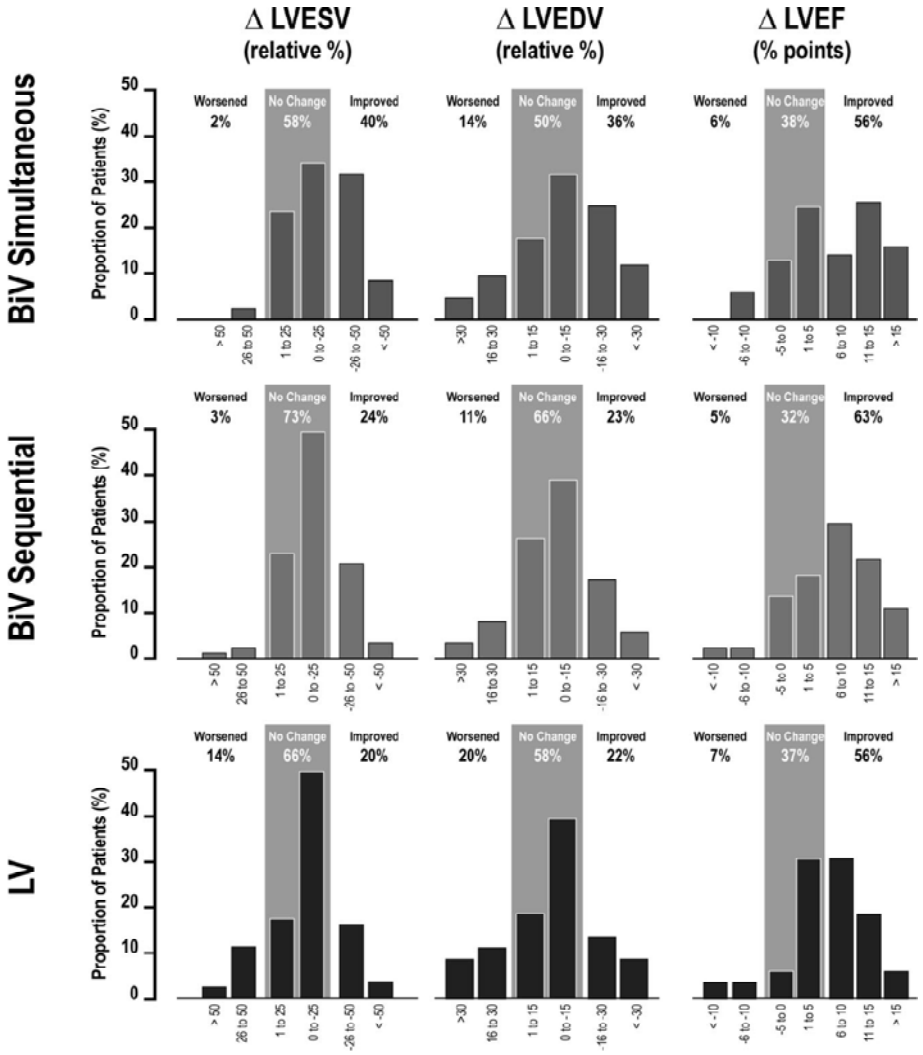
→ Favorable long-term outcome, **Reproducible at Different Centers**

→ Leading cause of death = **HF**,

→ Total mortality ↓~20%, **SD ↓96%** (HR 0.04, P<.002) **in ICD back-up** than CRT alone

Reduced Ventricular Volumes and Improved Systolic Function With **Cardiac Resynchronization Therapy**. A Randomized Trial Comparing Simultaneous Biventricular Pacing, Sequential Biventricular Pacing, and **Left Ventricular Pacing** (**DECREASE-HF**)

Circ 2007;115:2136



- DB-Random, 3-arm study
- 306 pt (III~IV), ≤ 35%, **≥150ms**
- 3 mo, **6 mo** F/U Echo

→ ↓LVESV & EDV

: greatest in simultaneous BiV

→ all showed EF↑

: more modest in LV alone

* Optimal VV delay = -0.333 x (RV-LV electrical dealy) - 20ms

on-going "**B-LEFT HF** study".

CRT in Chronic Afib

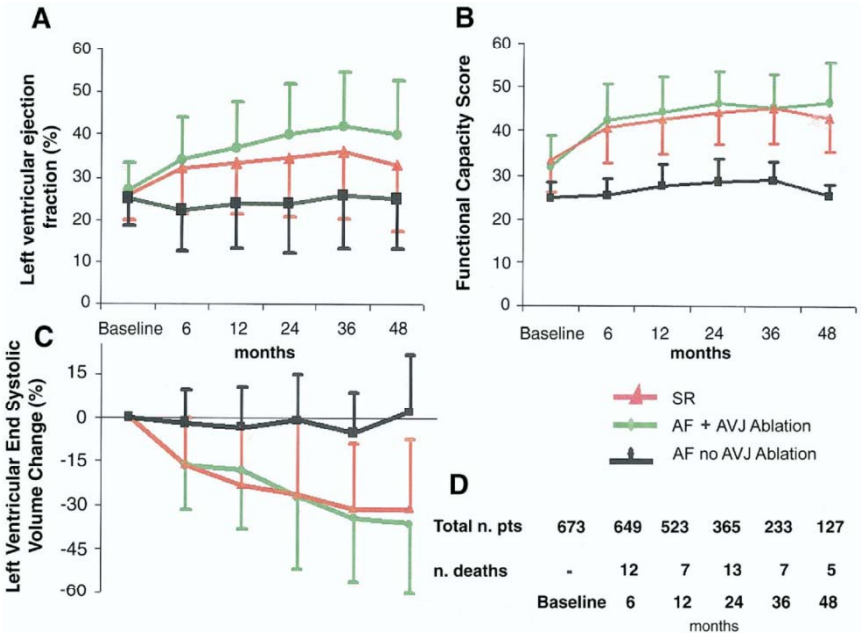
AF and Heart Failure

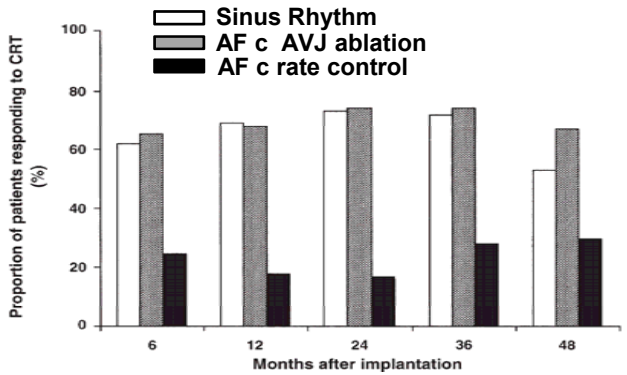
- Twin modern epidemics, often present concomitantly and directly predispose to each other.
- Prevalence of AF according to the NYHA Classes

  : 5% in I, 10~25% in II-III, ~50% in IV
- Incidence of AF in HF : up to 5% / yr
- Most of the CRT Trials → Excluded AF
- Several relatively small studies reports benefit of CRT in AF

  PAVE Post AVN ablation Evaluation, II~III (45%) : BiV. vs. RVP 6 mo → 6min walk↑, < ↓ EF in BiV.

Four-Year Efficacy of Cardiac Resynchronization Therapy on Exercise Tolerance and Disease Progression. The Importance of Performing Atrioventricular Junction Ablation in Patients With Atrial Fibrillation. Gasparini M, et al JACC 2006;48:734





- 162 AF / 673 HF (≤35%, ≥120ms, ≥ II)
- Biv. pacing % at 2 mo.

  > 85% → continue rate control (48)

  ≤ 85% → AVJ ablation (114)

  :Rate control G → Biv. pacing 88.2 ± 3.1%

  (Resting HR=76.4 ± 5.1bpm)

- Large and Sustained Long-term (~4 year) ↑ of EF and FC, **Similar to SR**, **only in AVJ ablation group**.

→ **Even relatively high % Biv. capture may be Inadequate.** *(Regularity~Pseudofusion)*

Unresolved Issues In CRT

- CRT in NYHA I ~ II Heart Failure : REVERSE(+) → MADIT-CRT, RAFT :ongoing
- CRT in Narrow QRS: Positive small studies(+) → RethinQ : Lack of benefit
- Should CRT be combined with ICD back-up?

  = Incremental benefit of CRT-D over CRT alone?

  → No Ongoing Randomized Controlled Trials

  (cf. CRT-D vs. ICD in HF I ~ II : MADIT-CRT :ongoing)

- Economic considerations on CRT → recently, positive reports(+)
- **Predictors of Response to CRT :**

  PROSPECT : Dysynchrony → additive effect (+)…….

수고 하셨습니다.