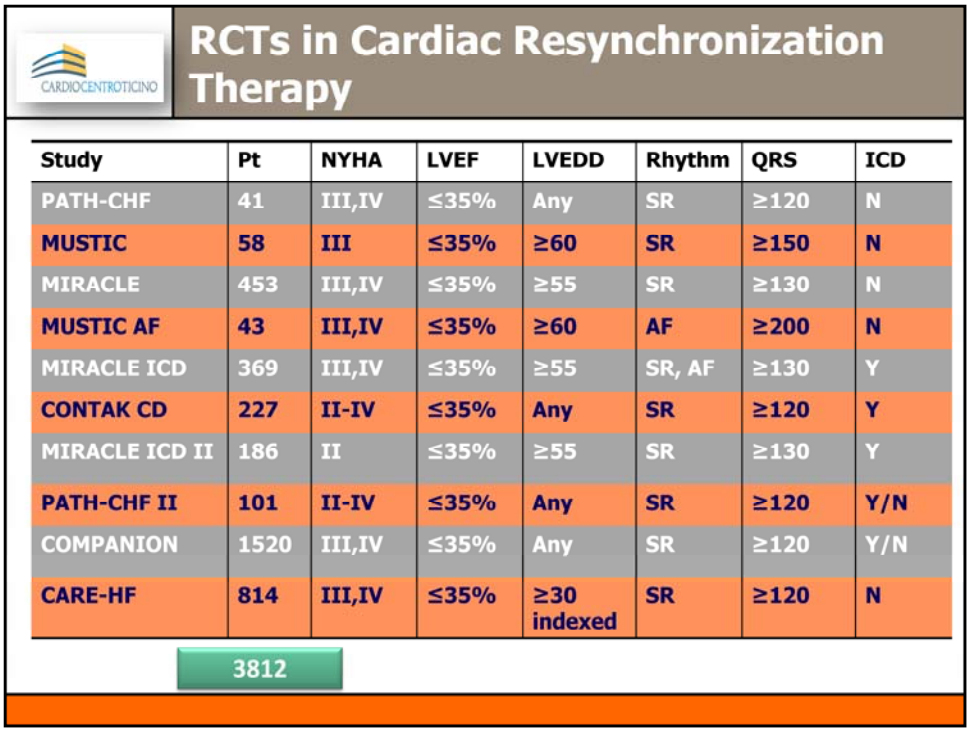
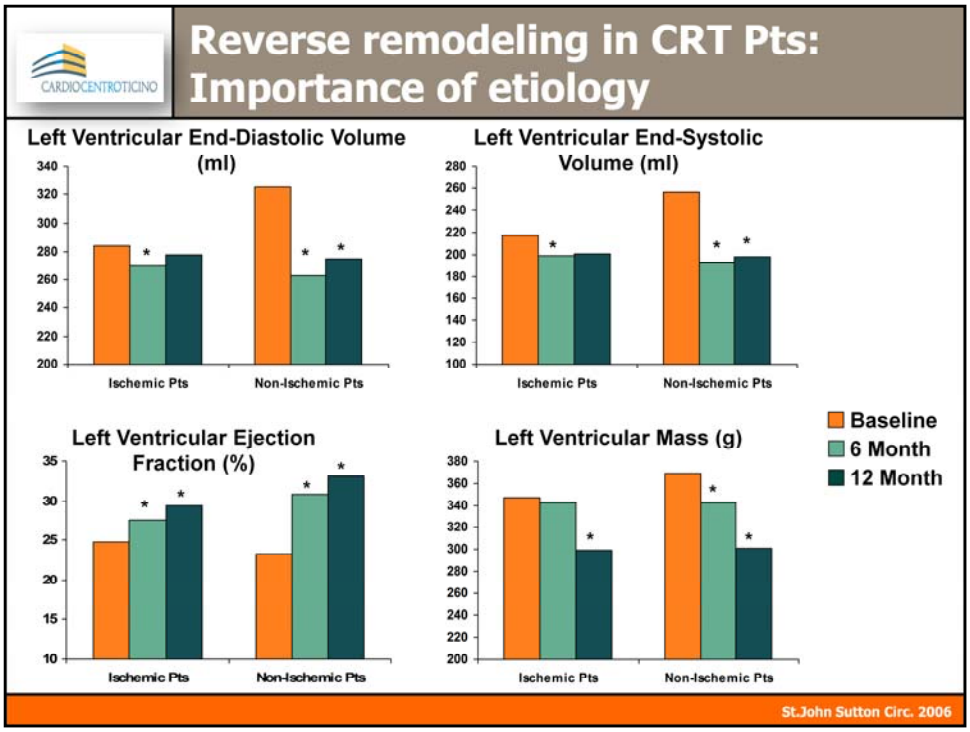
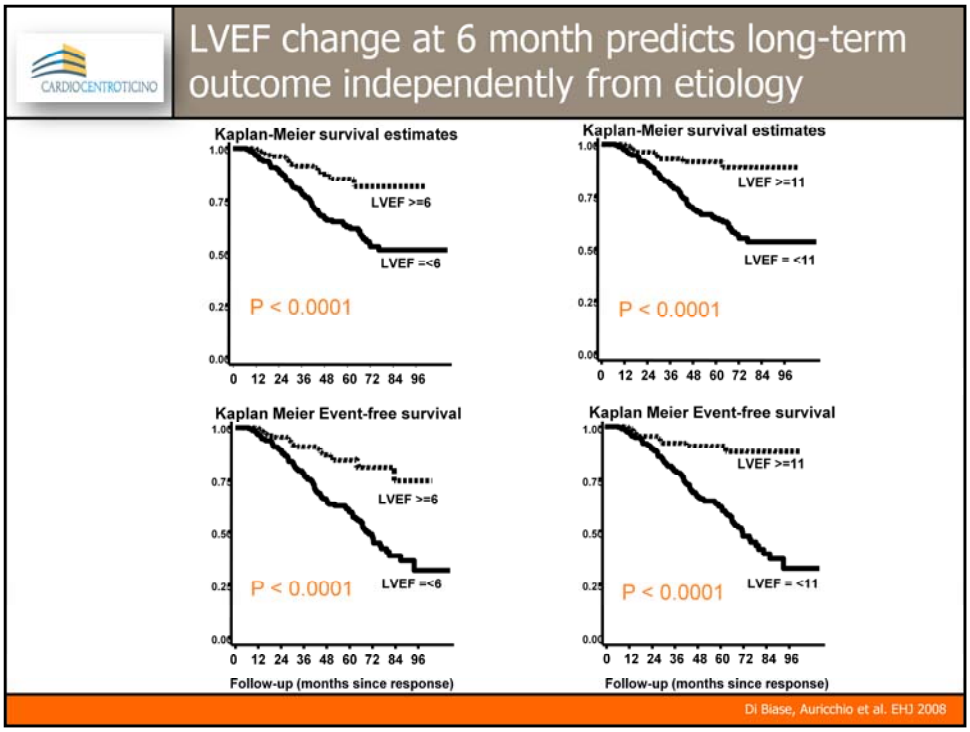


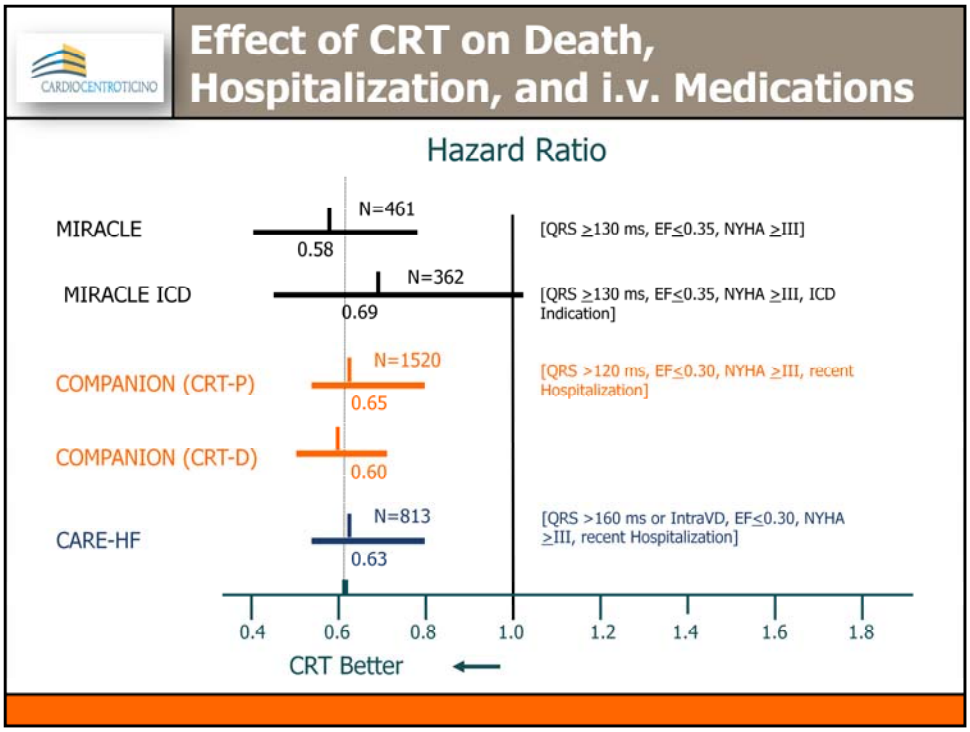
Several randomized controlled trials conducted in about 3800 patients have built the evidence for the use of cardiac resynchronization therapy in heart failure patients. Apart few exceptions such as CONTAK-CD study and PATH-CHF II study, all studies have included patients in advanced heart failure, New York Heart Association functional class III-IV, significantly reduced left ventricular ejection fraction and QRS duration above or equal 120 ms. The vast majority of patients were in sinus rhythm and about 50% of the patients were also treated with an implantable cardioverter-defibrillator.



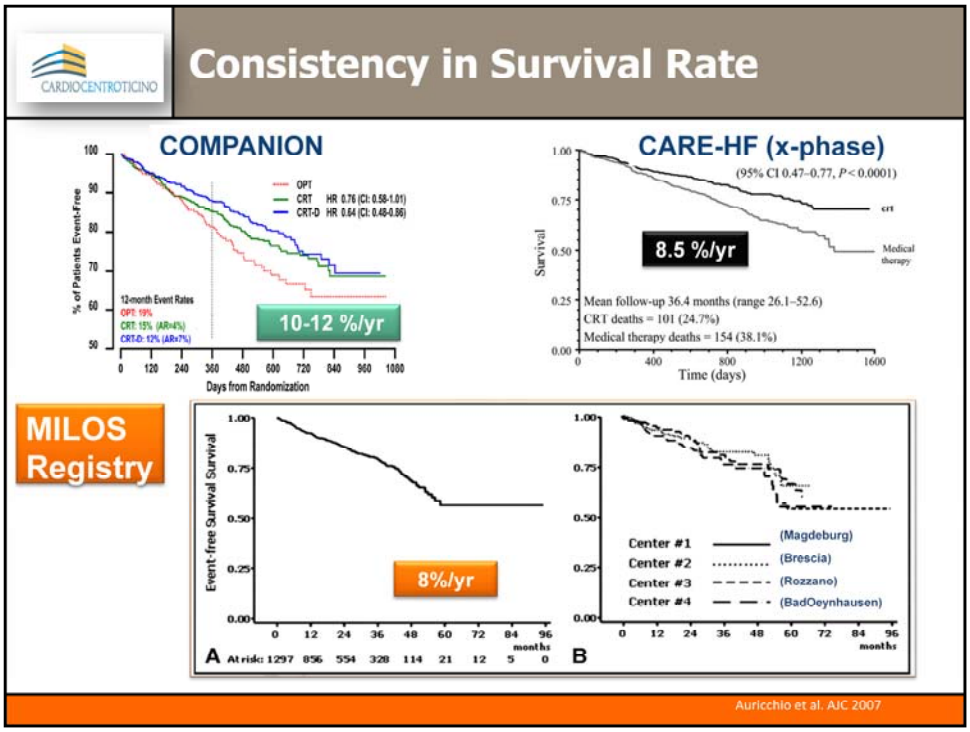
The effects of CRT on reverse remodeling are remarkable and extensive. Here is one of the many studies – the MIRACLE trial - showing that CRT induces a significant reduction of both left ventricular end-diastolic and end-systolic volume resulting in a large increase in left ventricular ejection fraction and reduction of left ventricular mass. Although differences in reverse left ventricular remodeling between patients with ischemic and non-ischemic cardiomyopathy have been consistently reported, this difference however was not translated survival difference.



Indeed, our data showed that when left ventricular ejection fraction increased at least 6 absolute points, there was no difference in survival of patients with ischemic or non-ischemic etiology. Of note, the change in left ventricular ejection fraction at 6 months predicted long-term (mean follow-up time about 3 and half year) survival. In this study, however, it was not possible to distinguish whether a different survival existed in those patients who had impressive change in left ventricular ejection fraction, >= 11 abolute points, compared to the other who had an in increase of at least 6 absolute points.



The 4 largest prospective randomized controlled trials conducted in heart failure patients which had mortality and/or hospitalization as primary end-point consistently showed that CRT had a very large and significant reduction in the total number of deaths, hospitalization rate and use of i.v. medications (inotropics, vasodilators, and diuretics). The hazard ratio of all these studies varied between 0.58 and 0.69 indicating a reduction of combined events of at least 35% to 40% in favor of CRT.



The impressive reduction of yearly mortality rate observed in prospective randomized controlled trials has been recently confirmed in the comparative analysis of the mortality rate in the Multicenter Longitudinal Observational Study (MILOS). There was great similarity in the patient characteristics of the 4 centers participating to the MILOS study; more importantly, the yearly all-cause mortality observed in the MILOS trial was 8%, thus being consistent with mortality rate of both COMPANION and CARE-HF study. MILOS study emphasizes that the results obtained in clinical randomized controlled studies are reproducible in daily practice.

Marginal Benefit in AF Patients

Table 2 Results of intention-to-treat analysis

		Right uni ventricular		Biventricular		Δ	*P*
		n	mean ± SD	n	mean ± SD		
Treatment arm 1	6 min walked test distance (m)	18	360 ± 101	18	389 ± 109	+29	
	Peak VO_2 (ml . kg^{-1} min^{-1})	17	13·9 ± 4·4	17	15·7 ± 4·1	+1·8	
	QOL score	21	35·9 ± 20·1	21	32·4 ± 21·8	−3·5	
Treatment arm 2	6 min walked test distance (m)	20	324·2 ± 98	20	332·5 ± 128·1	+8	
	Peak VO_2 (ml . kg^{-1} min^{-1})	15	12·8 ± 3·6	15	13·7 ± 3·9	+0·9	
	QOL score	18	41·5 ± 23·1	18	36·0 ± 19·5	−5·5	
Treatment arms 1+2	6 min walked test distance (m)	38	341 ± 100	38	359 ± 121	+18	ns
	Peak VO_2 (ml . kg^{-1} min^{-1})	32	13·4 ± 4·0	32	14·8 ± 4·1	+1·4	0·08
	QOL score	39	38·5 ± 21·4	39	34·1 ± 20·6	−4·4	ns
	Patient preference	39*	4	39	33		0·001

VO_2=oxygen uptake; QOL=quality of life; n=number of patients without missing data; *=2 patients did not indicate any preference.

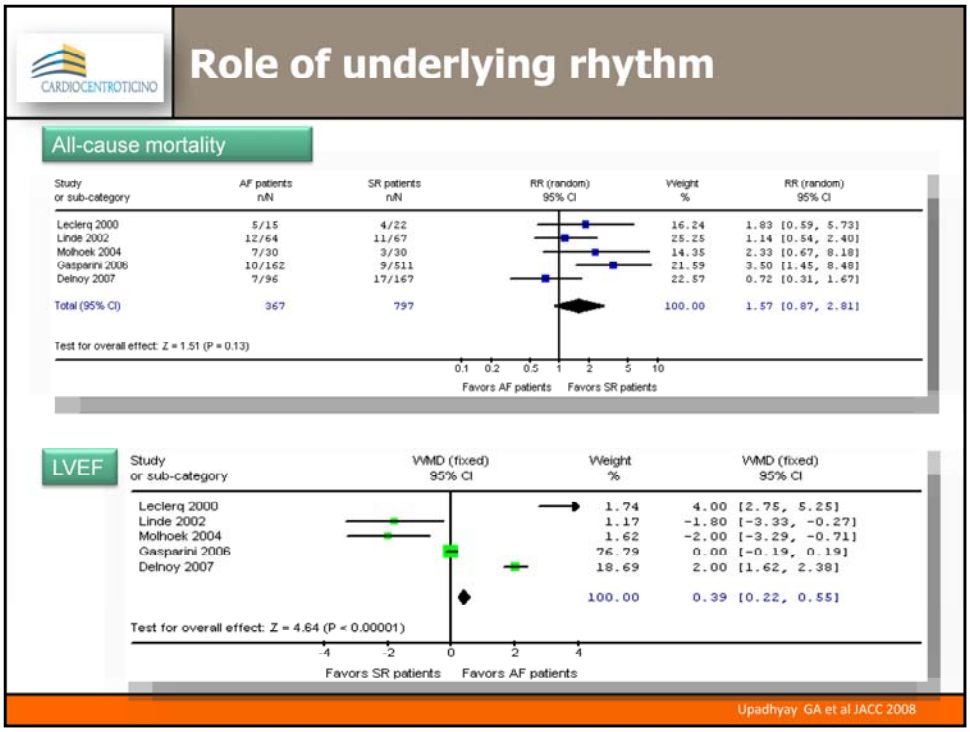
Table 3 Efficacy analysis set

		Right-univentricular		Biventricular		Δ	*P*
		n	mean ± SD	n	mean ± SD		
Treatment arm 1	6 min walked test distance (m)	18	360 ± 101	18	389 ± 109	+29	
	Peak VO_2 (ml . kg^{-1} min^{-1})	17	13·9 ± 4·4	17	15·7 ± 4·1	+1·8	
	QOL score	21	35·9 ± 20·1	21	32·4 ± 21·8	−3·5	
Treatment arm 2	6 min walked test distance (m)	16	323 ± 105	16	358 ± 109	+35	
	Peak VO_2 (ml . kg^{-1} min^{-1})	13	12·2 ± 3·1	13	13·8 ± 4·2	+1·6	
	QOL score	16	40·6 ± 24·3	16	35·1 ± 20·4	−5·5	
Treatment arms 1+2	6 min walked test distance (m)	34	342 ± 103	34	374 ± 108	+32	0·05
	Peak VO_2 (ml . kg^{-1} min^{-1})	30	13·2 ± 3·9	30	14·9 ± 4·2	+1·7	0·04
	QOL score	37	37·9 ± 21·8	37	33·6 ± 21	−4·3	0·11
	Patient preference	37	33	37	4		0·001

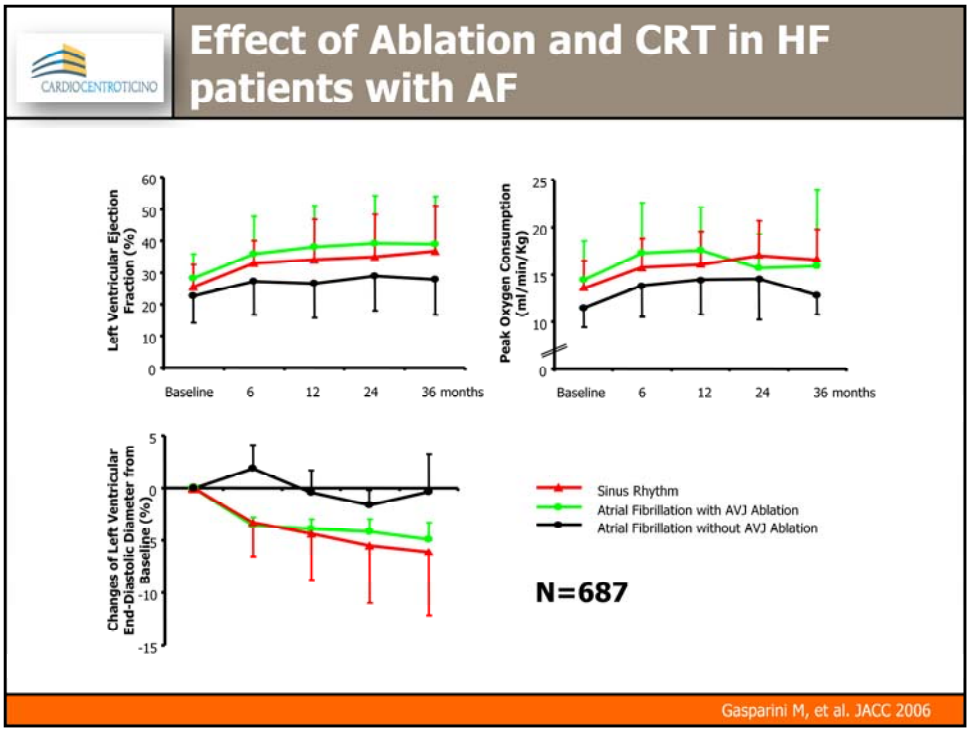
VO_2=oxygen uptake; QOL=quality of life; n=patients without missing data.

MUSTIC AF. Leclercq et al Eur Heart J 2002; 23: 1780

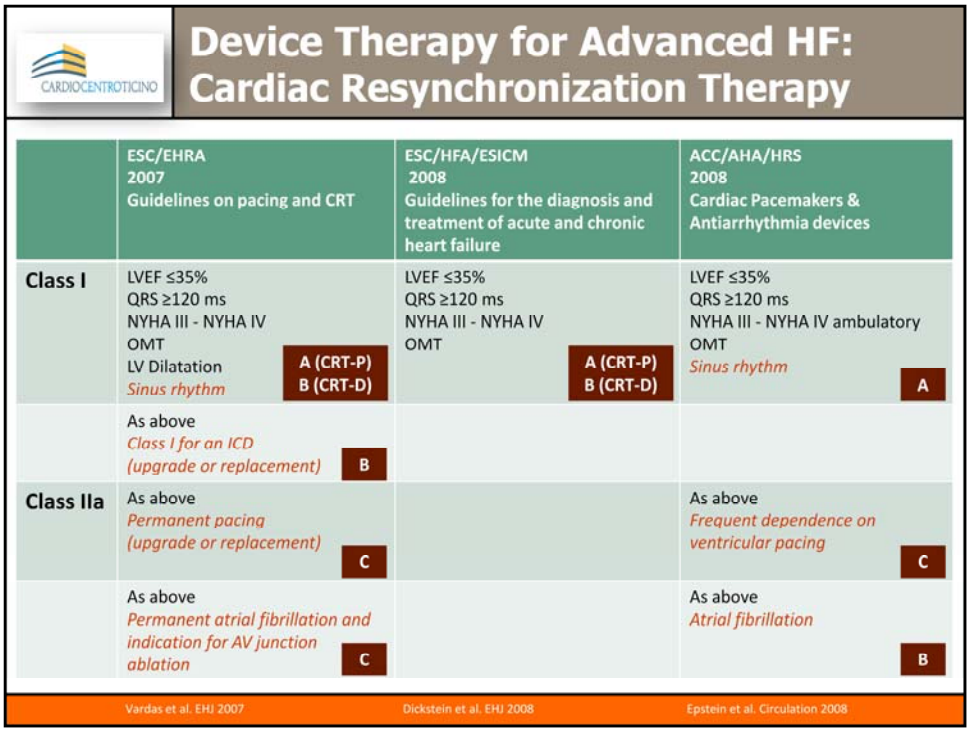
Although atrial fibrillation is frequently present in functional class NYHA III-IV, only one prospective randomized controlled study – the MUSTIC-AF study – has addressed this important group of patients. However, the results of the study were quite disappointing. Indeed, on both intention-to-treat analysis and efficacy analysis the effect of biventricular pacing was nearly indistinguishable from conventional right ventricular pacing.



In contrast, a recent meta-analysis using data collected in observational trials as well as in the MUSTIC-AF study included 367 atrial fibrillation patients and 797 sinus rhythm patients. The meta-analysis showed that both all-cause mortality and changes in left ventricular ejection fraction were of similar magnitude in patients with sinus rhythm or with atrial fibrillation. However, there was some heterogeneity in respect to changes in left ventricular ejection fraction.



In this respect, the data presented by Gasparini and our group showed that, in order to obtain a similar degree of reverse remodeling and change in exercise capacity in patients with atrial fibrillation as those in sinus rhythm, ablation of the atrioventricular junction should be performed. Indeed, although a good resting heart rate was successfully obtain with pacemaker programming and antiarryhthmic drugs in all atrial fibrillation patients in whom no ablation was performed, this was apparently not enough. Indeed, only 100% continuous biventricular pacing, as achieved by ablation of atrioventricular junction, was able to significantly improve functional, reverse remodeling, and survival outcome.

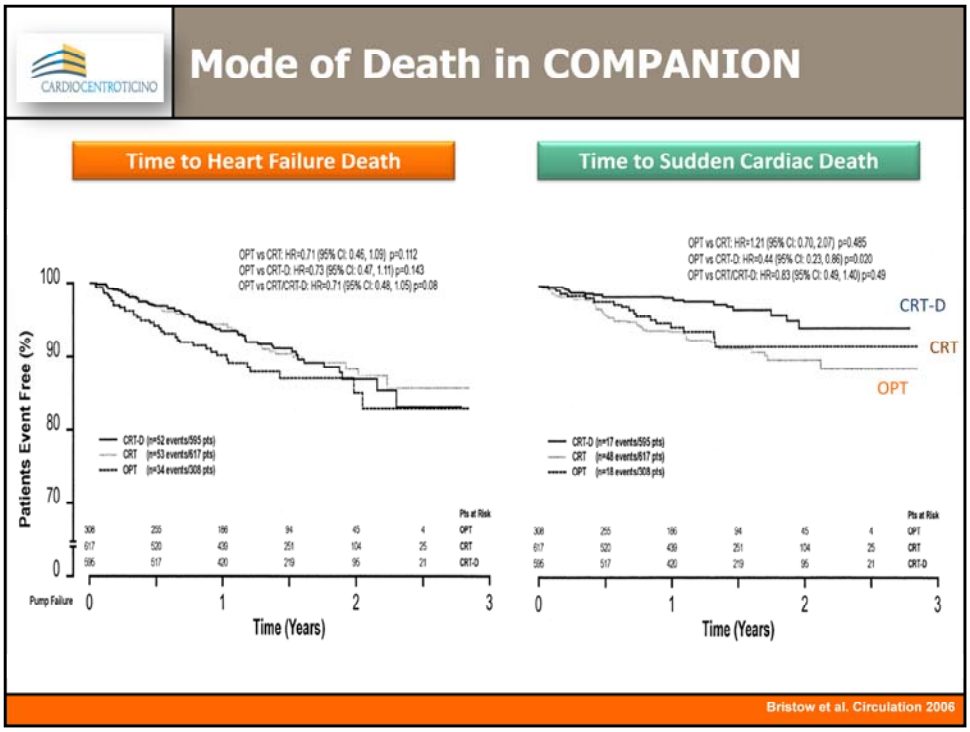


All these results represented the clinical evidence on which guidelines have been issued.

Clinical practice guidelines for cardiac resynchronization therapy (CRT) have recently been updated by both European and American scientific societies. These are largely consistent with respect to Class I and IIa recommendations.

For the first time, these guidelines have included two new groups of heart failure patients: patients with chronic atrial fibrillation and patients in whom frequent dependence on ventricular pacing is anticipated. Whilst these guidelines share common ground, there are also important differences. Prominent amongst these is that European guidelines distinguish between the levels of evidence for the two types of CRT: A for CRT-P (pacing only) and B for CRT-D (with implantable cardioverter-defibrillator back-up). This peculiar situation has arisen as a result of the lack of randomized, controlled, head-to-head comparisons of CRT-P and CRT-D. I will comment in a few moments on this apparent contradiction.

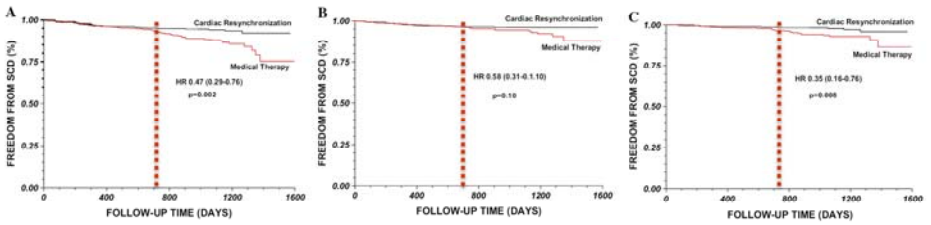
Another important difference relates to atrial fibrillation: while US guidelines consider CRT appropriate for patients with atrial fibrillation without distinction between paroxysmal, permanent or persistent, European guidelines recommend CRT only in patients with chronic atrial fibrillation who also undergo atrioventricular junction ablation.



The analysis of the mode of death in the COMPANION study showed that time to heart failure for both CRT-P and CRT-D was significantly longer than optimal medical therapy. In contrast, time to sudden cardiac death was longer only in those patients treated with CRT-D; patients treated with CRT-P showed no difference to best medical therapy. This result however conflicted with data from the CARE-HF study

Effect of CRT-P on SCD (CARE-HF)

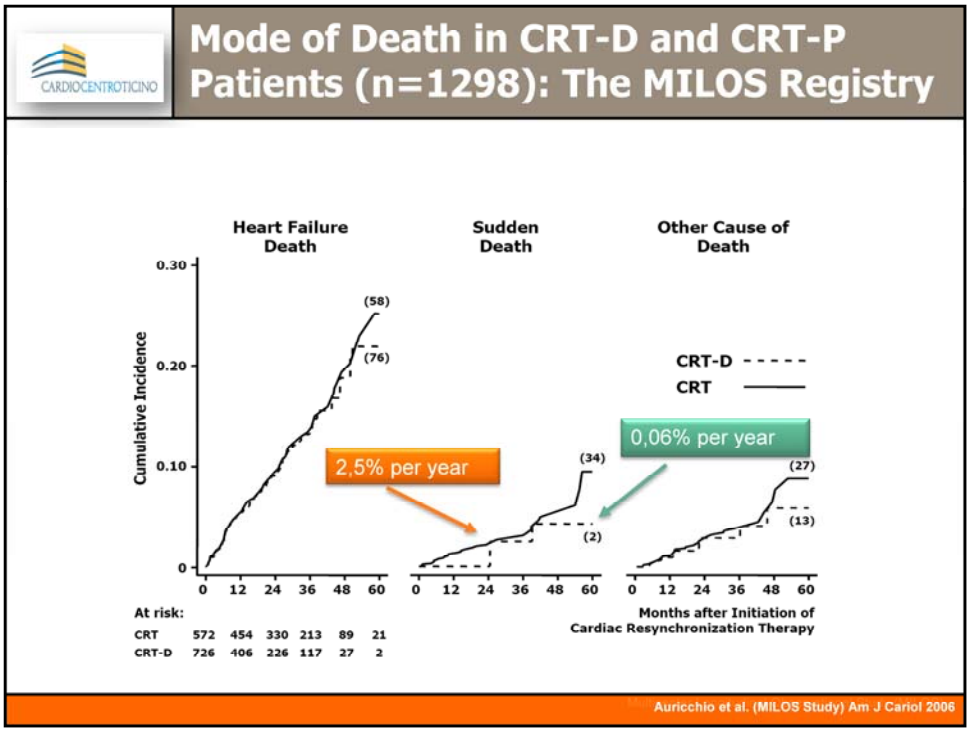
Definitive SCD | Probable SCD | Possible SCD



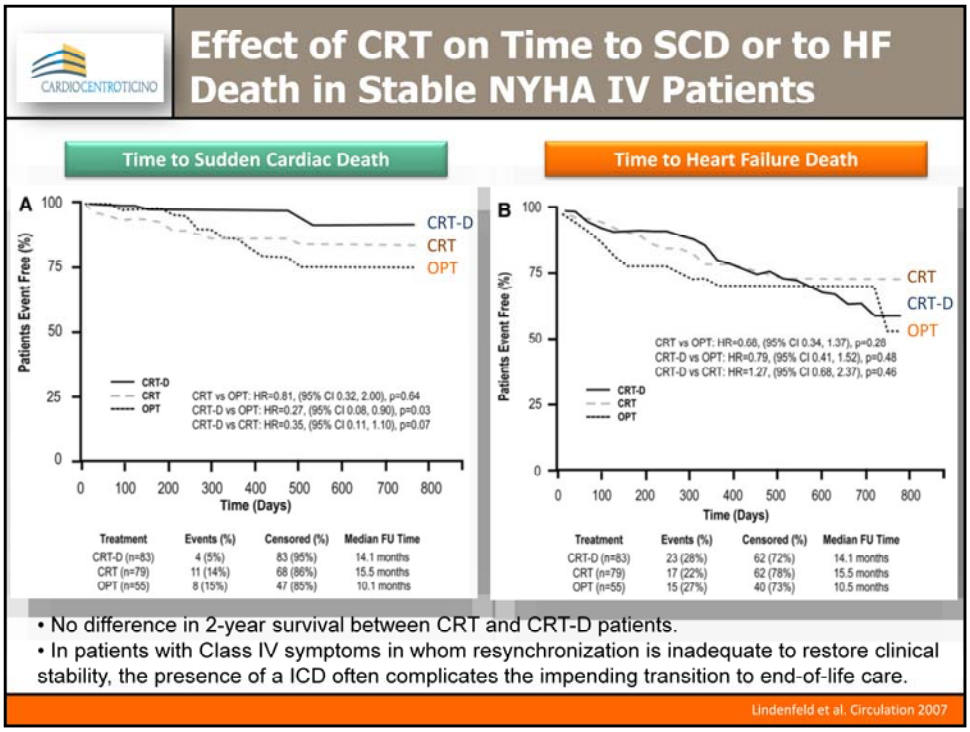
- Definite: witnessed sudden unexpected collapse with documented arrhythmia (classified as "arrhythmic");
- Probable: witnessed sudden unexpected collapse without documented arrhythmia (classified as "unknown but probably arrhythmic"); and
- Possible: unwitnessed sudden unexpected death (classified as "unknown cause but known mode of death") in the cardiovascular category.

Uretsky et al. J Cardiac Fail 2008

In the CARE-HF study, the probability of sudden cardiac death in CRT patients was extremely low. These intriguing findings indicated that CRT-P alone may be able to significantly reduce sudden cardiac death.



Although a prospective randomized study comparing CRT-P and CRT-D is still missing so that the dilemma whether to use one or the other device remains, in the MILOS registry there are however indirect observation that suggest that CRT-D is probably better than CRT-P. The probability of dying suddenly was in general extremely low and close to that observed in the CARE-HF study. However, because the MILOS registry included patients who were treated with CRT-P due to lack of device with CRT-D capabilities, the yearly sudden death rate was 2.5% compared to heart failure patients who were implanted when CRT-D device were available. In this latter group of patients the yearly sudden death rate was about 40 times less. As in the COMPANION study, heart failure rate was similar in CRT-D and CRT-P patients.

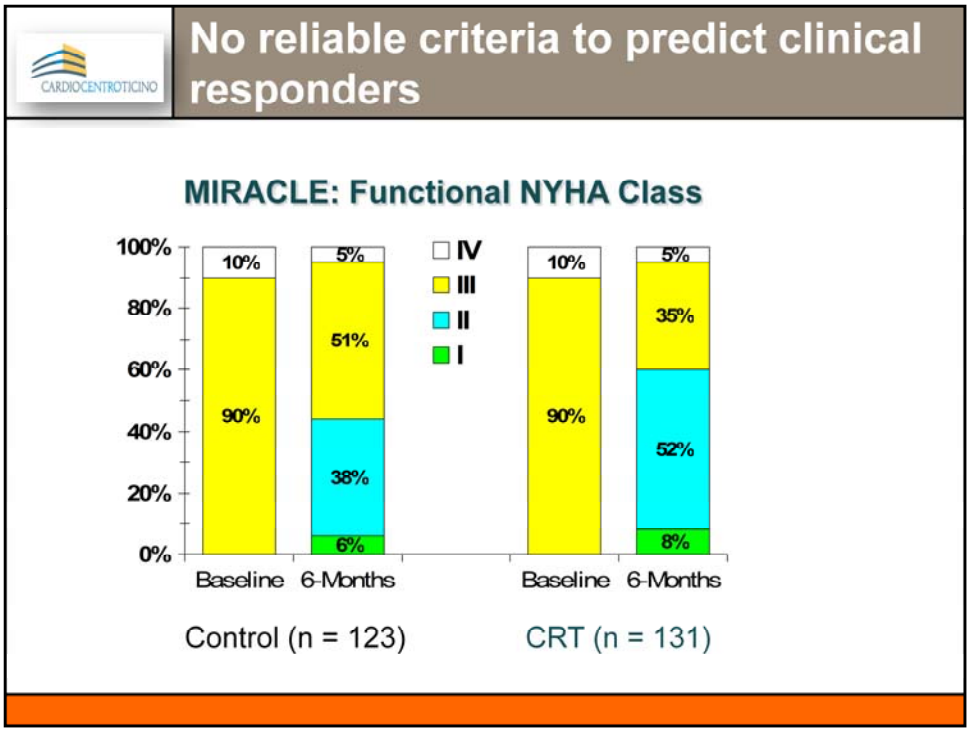


Patients with Class IV symptoms of heart failure with prolonged QRS duration and optimal lead placement may return to Class III status or better for both function and survival, at which point prevention of sudden death again becomes a relevant goal.

Information on Class IV patients is limited because only 10% of the almost 4000 patients in resynchronization trials have had Class IV symptoms. In the COMPANION trial, there were Class IV patients for whom resynchronization improved QOL and reduced rehospitalization and mortality; however, these patients were stable at home before study entry and may not represent typical Class IV patients. Even in this selected group, there was no difference in 2-year survival between CRT patients with and without the defibrillator feature.

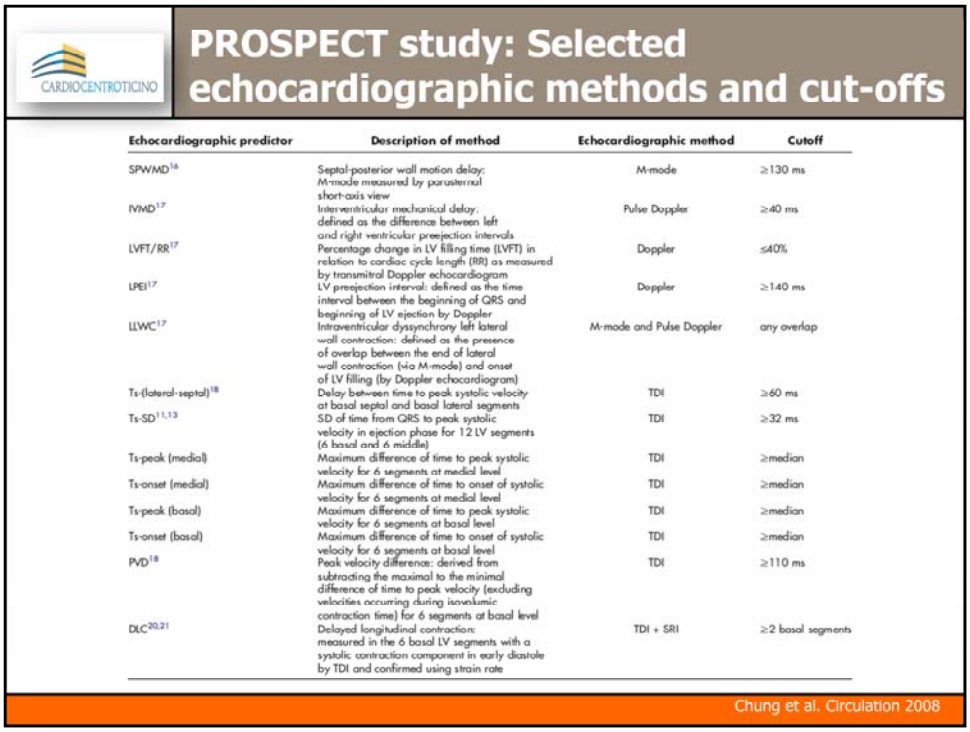
In patients with Class IV symptoms in whom resynchronization is inadequate to restore clinical stability, the presence of a defibrillator often complicates the impending transition to end-of-life care.

There is however the issue of the precise prediction of which patient will remain in functional class IV and which patient will receive significant benefit from CRT.



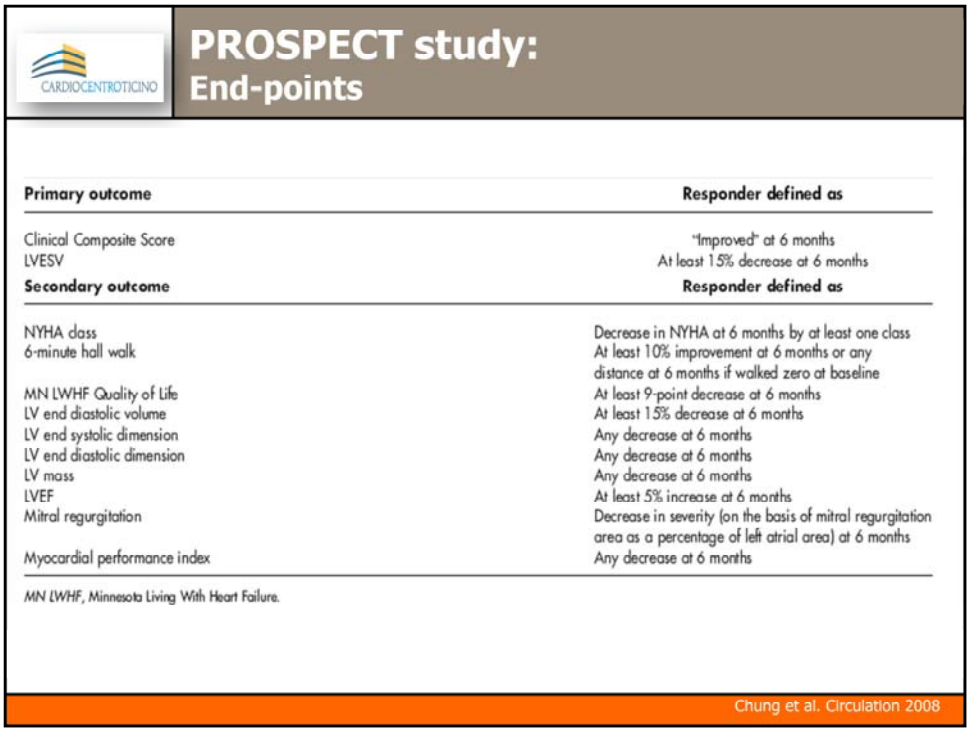
As we know from all randomized controlled studies, about one third of the patients continue to be symptomatic after CRT. As one example, the data from MIRACLE study showed that about 5% of the patients remained in functional class IV and about 35% remained in functional class III after CRT.

One of the frequently quoted reason for the lack of improvement after CRT is the fact that some heart failure patients, despite the fact they present a QRS duration above 120 ms, do not present mechanical dyssynchrony.

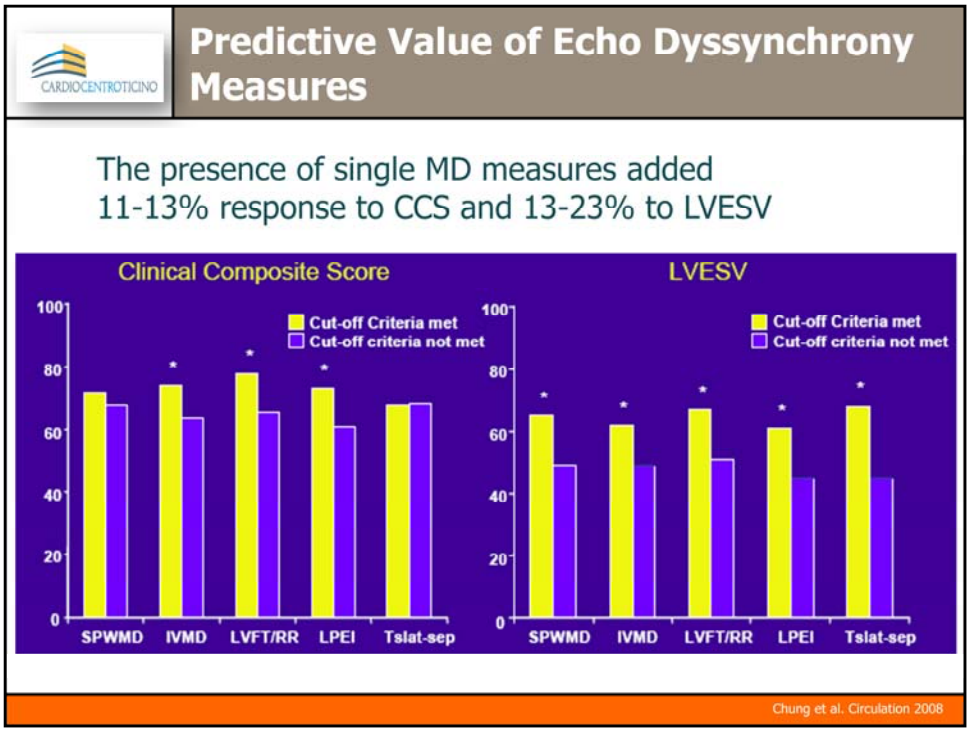


Echocardiographic predictor	Description of method	Echocardiographic method	Cutoff
SPWMD[16]	Septal-posterior wall motion delay: M-mode measured by parasternal short-axis view	M-mode	≥130 ms
IVMD[17]	Interventricular mechanical delay: defined as the difference between left and right ventricular preejection intervals	Pulse Doppler	≥40 ms
LVFT/RR[17]	Percentage change in LV filling time (LVFT) in relation to cardiac cycle length (RR) as measured by transmitral Doppler echocardiogram	Doppler	≤40%
LPEI[17]	LV preejection interval: defined as the time interval between the beginning of QRS and beginning of LV ejection by Doppler	Doppler	≥140 ms
LLWC[17]	Intraventricular dyssynchrony left lateral wall contraction: defined as the presence of overlap between the end of lateral wall contraction (via M-mode) and onset of LV filling (by Doppler echocardiogram)	M-mode and Pulse Doppler	any overlap
Ts-(lateral-septal)[18]	Delay between time to peak systolic velocity at basal septal and basal lateral segments	TDI	≥60 ms
Ts-SD[11,13]	SD of time from QRS to peak systolic velocity in ejection phase for 12 LV segments (6 basal and 6 middle)	TDI	≥32 ms
Ts-peak (medial)	Maximum difference of time to peak systolic velocity for 6 segments at medial level	TDI	≥median
Ts-onset (medial)	Maximum difference of time to onset of systolic velocity for 6 segments at medial level	TDI	≥median
Ts-peak (basal)	Maximum difference of time to peak systolic velocity for 6 segments at basal level	TDI	≥median
Ts-onset (basal)	Maximum difference of time to onset of systolic velocity for 6 segments at basal level	TDI	≥median
PVD[18]	Peak velocity difference: derived from subtracting the maximal to the minimal difference of time to peak velocity (excluding velocities occurring during isovolumic contraction time) for 6 segments at basal level	TDI	≥110 ms
DLC[20,21]	Delayed longitudinal contraction: measured in the 6 basal LV segments with a systolic contraction component in early diastole by TDI and confirmed using strain rate	TDI + SRI	≥2 basal segments

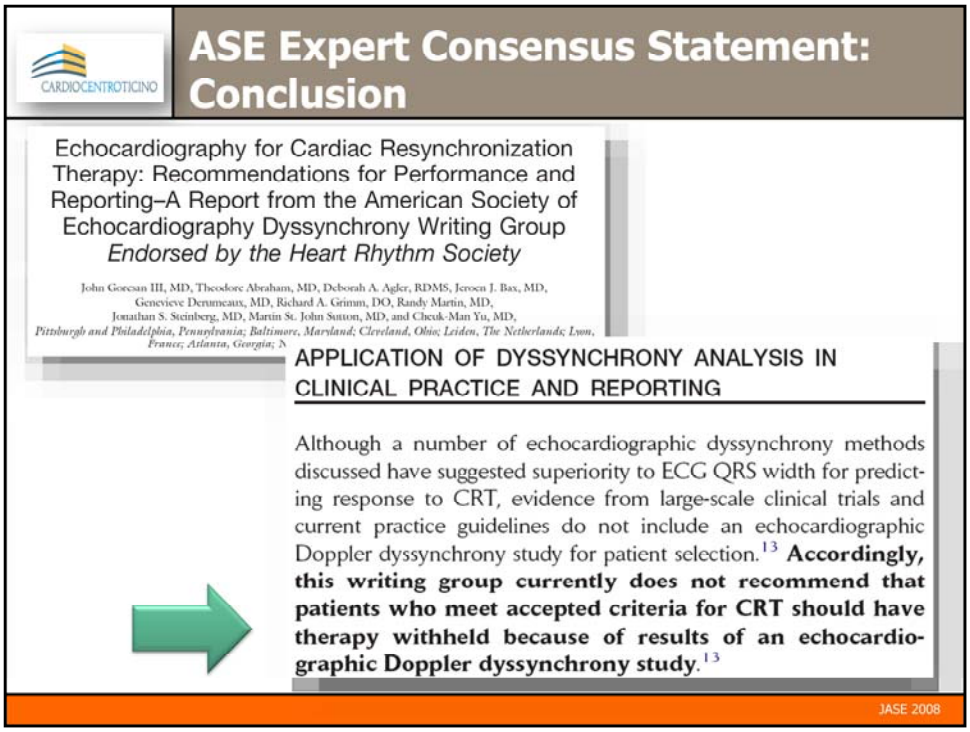
Several echocardiographic methods have been proposed to evaluate mechanical dyssynchrony and they have brought up the idea that only when mechanical dyssychrony is present and detectable by an echocardiographic technique the response to CRT is significantly superior to those observed in patients without mechanical dyssynchrony. Only recently a prospective, multicenter, observational controlled study – the PROSPECT study – has been conducted. Patients included in this trial underwent extensive echocardiographic examination including multiple, simple, as well as advanced echocardiographic techniques for detecting mechanical dyssynchrony.



The study had as primary outcome a clinical composite end-point and significant reduction in reverse remodeling. Multiple secondary end-points were also selected. The basic idea of the study was that in those patients in whom mechanical dyssychrony was detected the clinical composite score and the amount of reverse remodeling should be much higher than those patients without mechanical dyssynchrony.

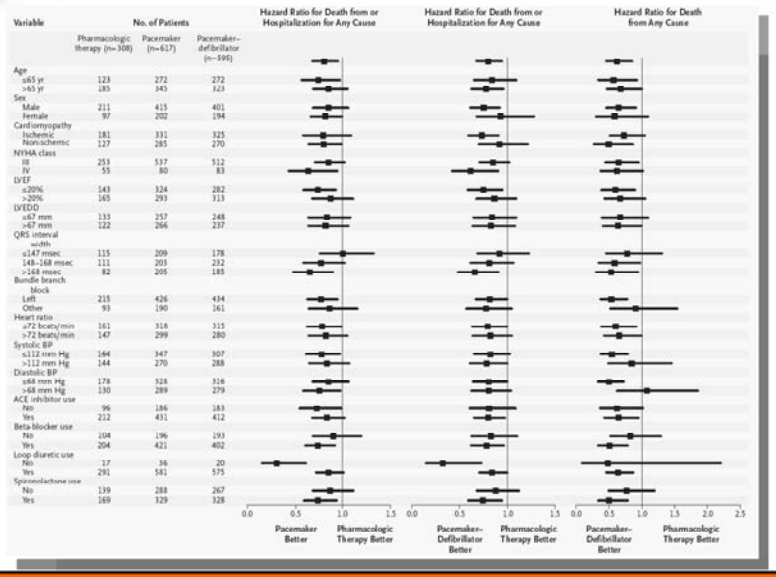


Against any expectation, there was no echocardiographic parameter which scored better than any other. Overall the presence of single mechanical dyssynchrony added little to clinical composite end-point. Although there was a trend towards a higher frequency of patients with significant reverse remodeling when mechanical dyssynchrony was present, all indexes equally perfomed. This study questioned the real value of echocardiographic evaluation of mechanical dyssynchrony in heart failure patients candidate to CRT.



For this reason, the conclusion of a recent report from the American Society of Echocardiography Dyssynchrony Writing Group was that patients who meet accepted (electrocadiographic) criteria for CRT should not have therapy withheld because of results of an echocardiographic Doppler dyssynchrony study. This view is shared by guideline committee members who did not include dyssynchrony in the latest reccomendations.

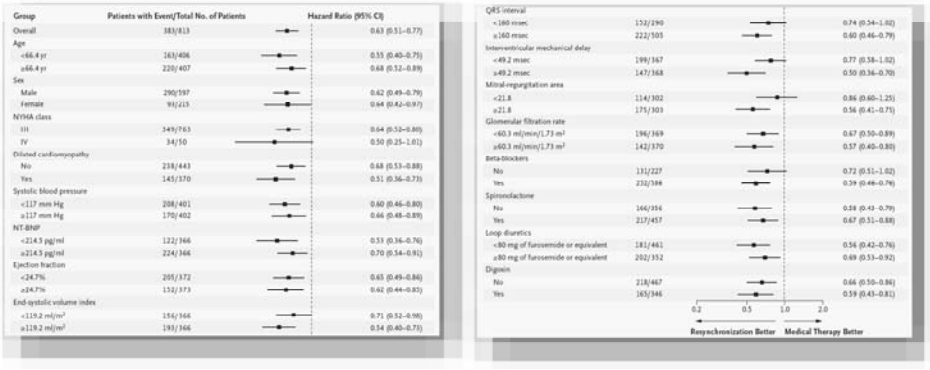
COMPANION Trial: All subgroups equally benefited



Bristow et al. NEJM 2005

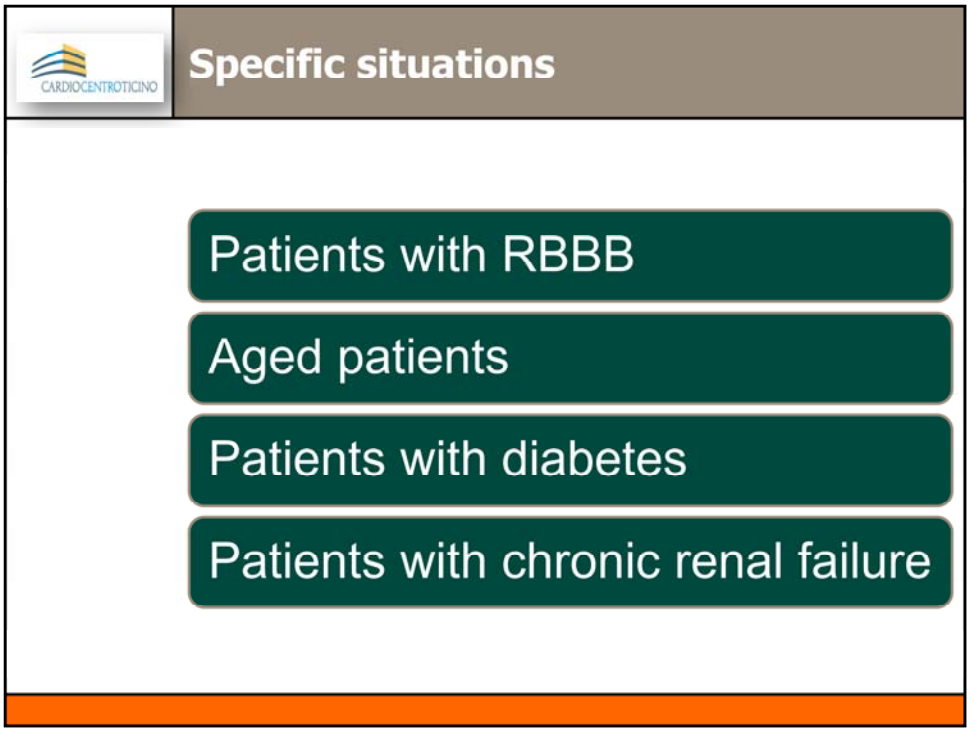
Although both COMPANION study

CARE-HF: All subgroups equally benefited

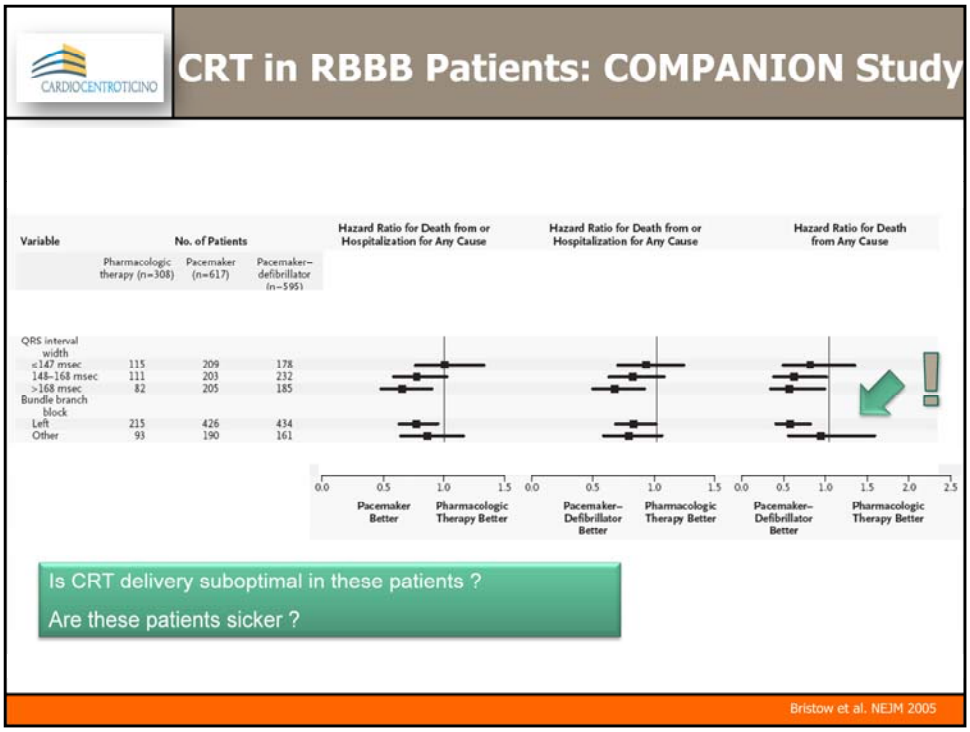


Cleland et al. NEJM 2005

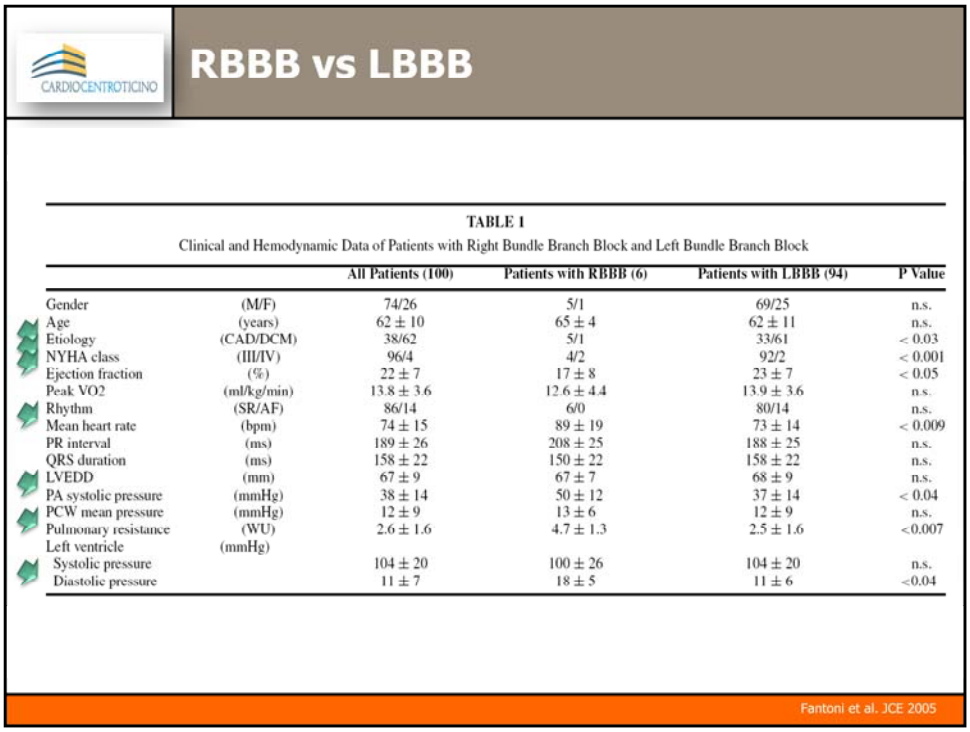
and CARE-HF studies showed that all subgroups of these prospectively randomized trials equally benefited of CRT,



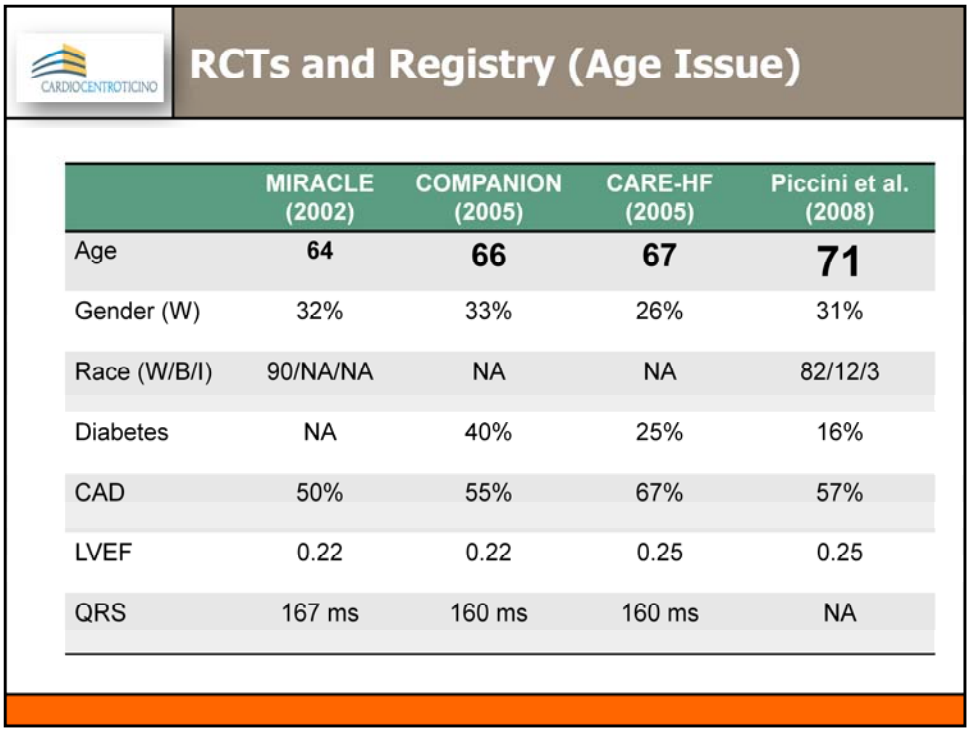
There are some specific situations in which the value of CRT is still unclear. Among the others, these four listed clinical situations are probably the most common and important ones which deserve more attention.



Patients with left bundle branch block is the largest group of patients usually treated with CRT. About 20% of heart failure patients candidate to CRT shows a right bundle branch block QRS complex. The question was whether this latter group of patient equally benefited of CRT. The data collected in the COMPANION study suggested that patients with RBBB tend to have less survival benefit than patients with RBBB. Because patients with right bundle branch block usually have different electrical activation sequence, it is entirely possible that “conventional” CRT is suboptimal in these patients. Alternatively, these patients may be sicker than patients with left bundle branch block.

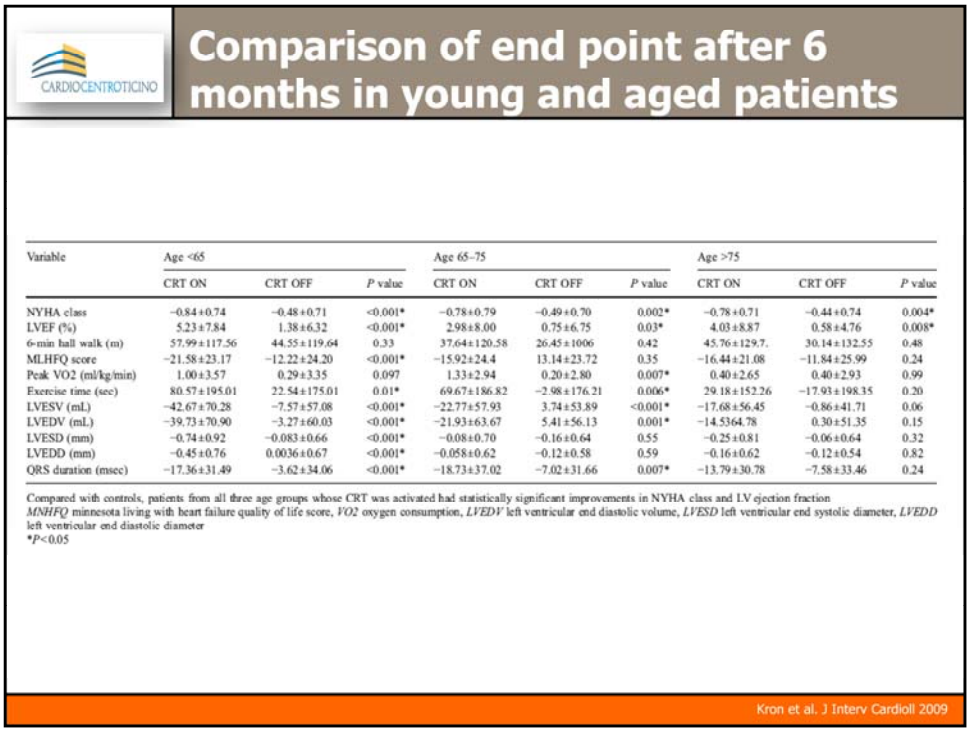


This hypothesis is apparently substantiated by findings of a small, non-controlled, observational trial by Fantoni et al. These authorse showed that patients with right bundle branch block have more frequently severe coronary artery disease, larger left and right ventricles, higher pulmonary pressures and resistance, and capillary wedge pressure.



	MIRACLE (2002)	COMPANION (2005)	CARE-HF (2005)	Piccini et al. (2008)
Age	64	66	67	71
Gender (W)	32%	33%	26%	31%
Race (W/B/I)	90/NA/NA	NA	NA	82/12/3
Diabetes	NA	40%	25%	16%
CAD	50%	55%	67%	57%
LVEF	0.22	0.22	0.25	0.25
QRS	167 ms	160 ms	160 ms	NA

Aged patients are usually underrepresented in randomized controlled trials, but they represent a significant, and growing proportion of heart failure patients. This slide shows, for example, that the mean age of patients included in the MIRACLE trial, the COMPANION study, and the CARE-HF study are significantly lower than the mean age of heart failure patients usually admitted in US hospitals.

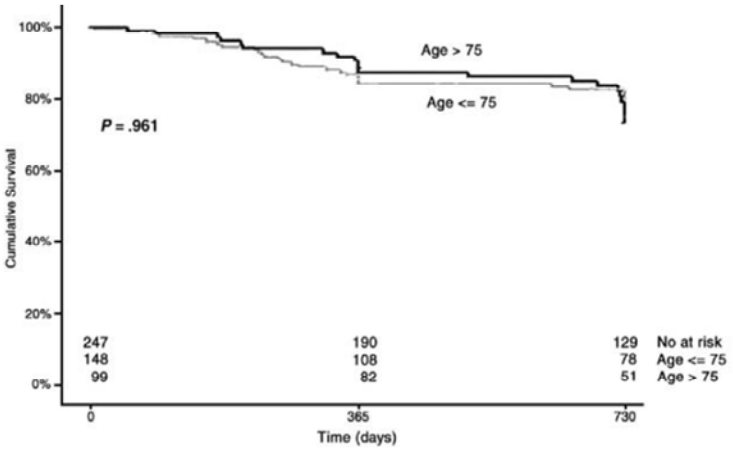


Variable	Age <65			Age 65–75			Age >75		
	CRT ON	CRT OFF	*P* value	CRT ON	CRT OFF	*P* value	CRT ON	CRT OFF	*P* value
NYHA class	−0.84±0.74	−0.48±0.71	<0.001*	−0.78±0.79	−0.49±0.70	0.002*	−0.78±0.71	−0.44±0.74	0.004*
LVEF (%)	5.23±7.84	1.38±6.32	<0.001*	2.98±8.00	0.75±6.75	0.03*	4.03±8.87	0.58±4.76	0.008*
6-min hall walk (m)	57.99±117.56	44.55±119.64	0.33	37.64±120.58	26.45±1006	0.42	45.76±129.7.	30.14±132.55	0.48
MLHFQ score	−21.58±23.17	−12.22±24.20	<0.001*	−15.92±24.4	13.14±23.72	0.35	−16.44±21.08	−11.84±25.99	0.24
Peak VO2 (ml/kg/min)	1.00±3.57	0.29±3.35	0.097	1.33±2.94	0.20±2.80	0.007*	0.40±2.65	0.40±2.93	0.99
Exercise time (sec)	80.57±195.01	22.54±175.01	0.01*	69.67±186.82	−2.98±176.21	0.006*	29.18±152.26	−17.93±198.35	0.20
LVESV (mL)	−42.67±70.28	−7.57±57.08	<0.001*	−22.77±57.93	3.74±53.89	<0.001*	−17.68±56.45	−0.86±41.71	0.06
LVEDV (mL)	−39.73±70.90	−3.27±60.03	<0.001*	−21.93±63.67	5.41±56.13	0.001*	−14.5364.78	0.30±51.35	0.15
LVESD (mm)	−0.74±0.92	−0.083±0.66	<0.001*	−0.08±0.70	−0.16±0.64	0.55	−0.25±0.81	−0.06±0.64	0.32
LVEDD (mm)	−0.45±0.76	0.0036±0.67	<0.001*	−0.058±0.62	−0.12±0.58	0.59	−0.16±0.62	−0.12±0.54	0.82
QRS duration (msec)	−17.36±31.49	−3.62±34.06	<0.001*	−18.73±37.02	−7.02±31.66	0.007*	−13.79±30.78	−7.58±33.46	0.24

Compared with controls, patients from all three age groups whose CRT was activated had statistically significant improvements in NYHA class and LV ejection fraction
MNHFQ minnesota living with heart failure quality of life score, *VO2* oxygen consumption, *LVEDV* left ventricular end diastolic volume, *LVESD* left ventricular end systolic diameter, *LVEDD* left ventricular end diastolic diameter
**P*<0.05

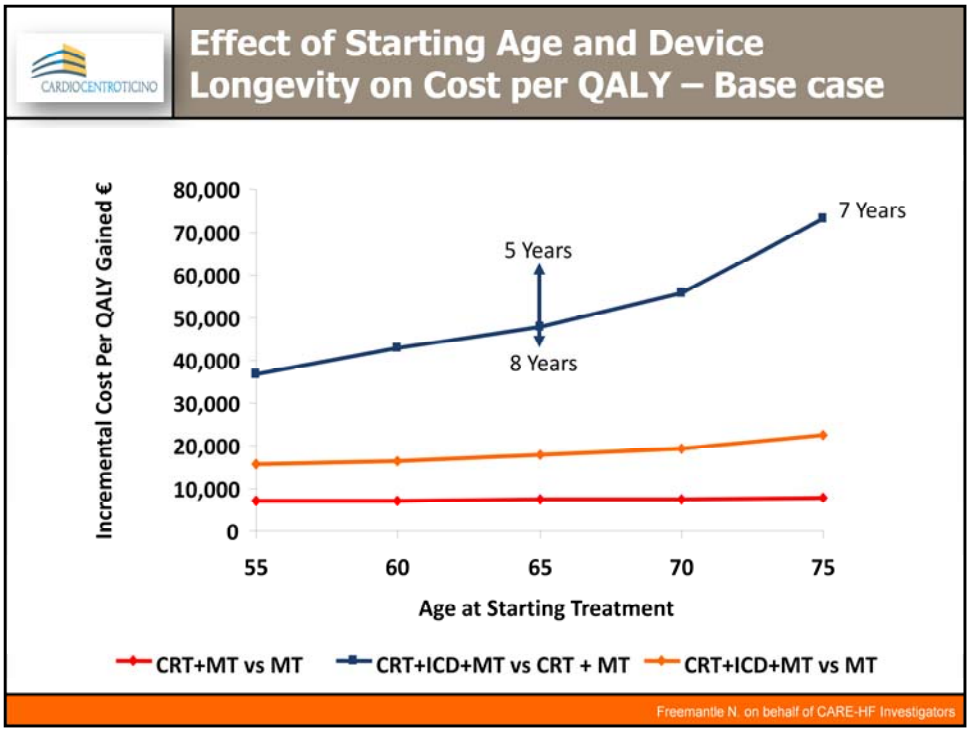
As shown in this slide, although there was a trend toward less benefit in patients older than 75 years compared to younger patients, still there was an advantage to treat aged patients with CRT.

Outcome of young and aged patients

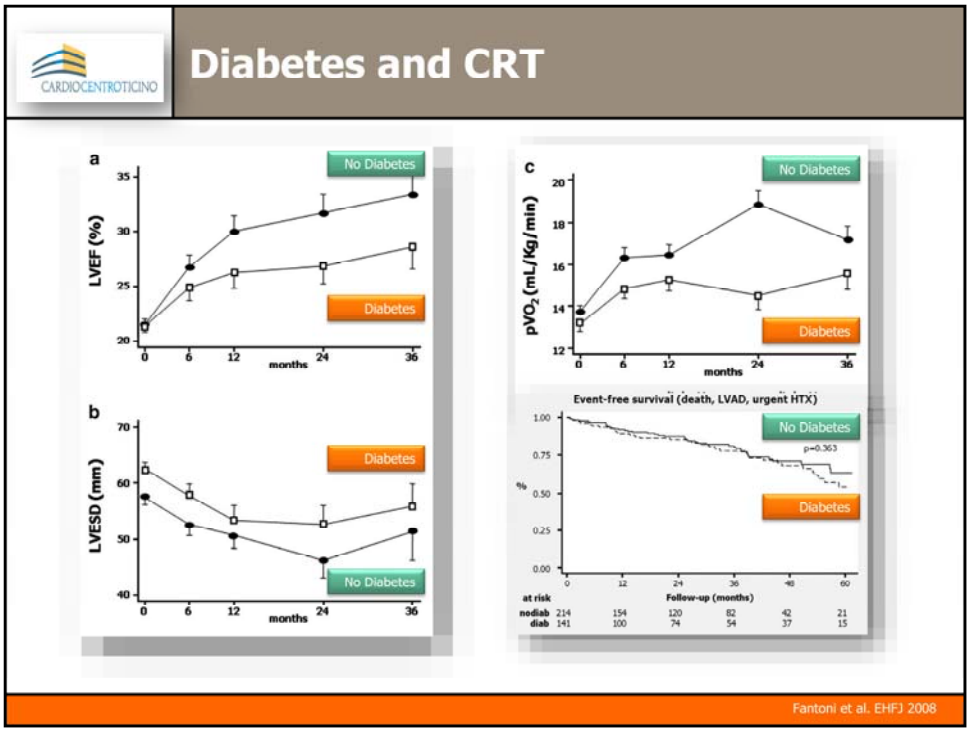


Delnoy et al AHJ 2008

Similarly, the survival rate of both young and aged patiens treated with CRT however seem to be similar.



As far as the type of device is concerned, we should note that the incremental cost per year of quality of life gained varies significantly depending from the age at starting the treatment and longevity of the device. Although both CRT-P and CRT-D have a very low incremental cost per QALY gained compared to optimal drug therapy, it is obvious that the use of CRT-D versus CRT-P is characterized by a significant hypothetical and never tested incremental cost per QALY gained. Moreover, if the device has a longevity of 5 years rather than the expected 7 years, the incremental cost significantly increases, whereas even if device longevity increases one year there is little reduction.



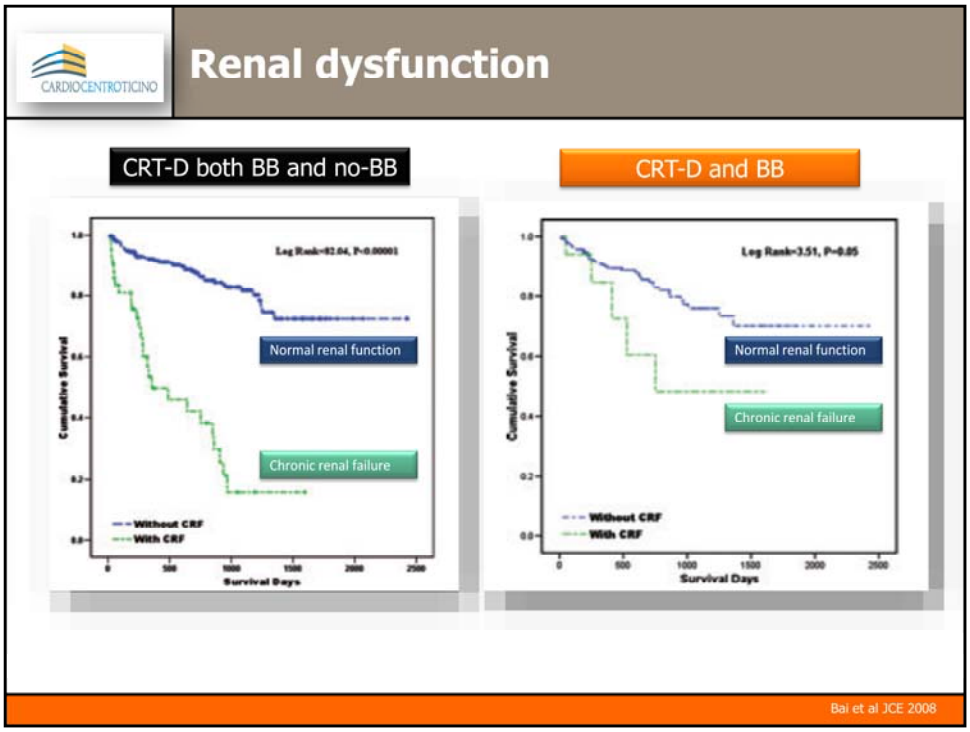
Patients with diabetes represent about one quarter of all patients treated with CRT. As shown by these data, although patients with diabetes had less reverse remodeling and lower increase in peak oxygen consumption, the survival was impressively similar.

Diabetes and CRT

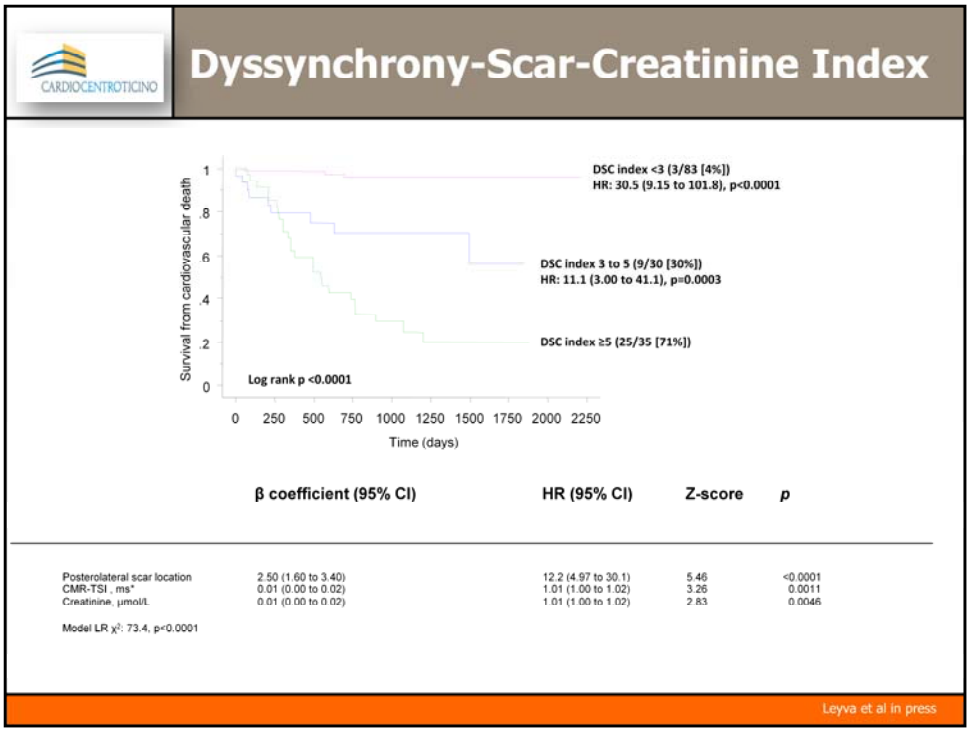
Outcome	Diabetic patients: Medical therapy	Diabetic patients: Medication + CRT	Nondiabetic patients: Medical therapy	Nondiabetic patients: Medication + CRT	*P* (interaction between CRT and diabetes)
n	101	106	303	303	
End points					
Death from any cause or unplanned hospitalization for a cardiovascular event	64 (63.4)	43 (40.6)	160 (53.0)	116 (38.3)	0.39
Death from any cause or unplanned hospitalization with worsening heart failure	54 (53.5)	35 (33.0)	137 (45.4)	83 (27.4)	0.91
Other serious adverse events					
Myocardial infarction	30 (29.7)	43 (40.6)	100 (33.1)	106 (35.0)	0.24
Stroke, transient ischemic attack	3 (3.0)	3 (2.8)	6 (2.0)	3 (1.0)	0.55

Diabetes Care 2007

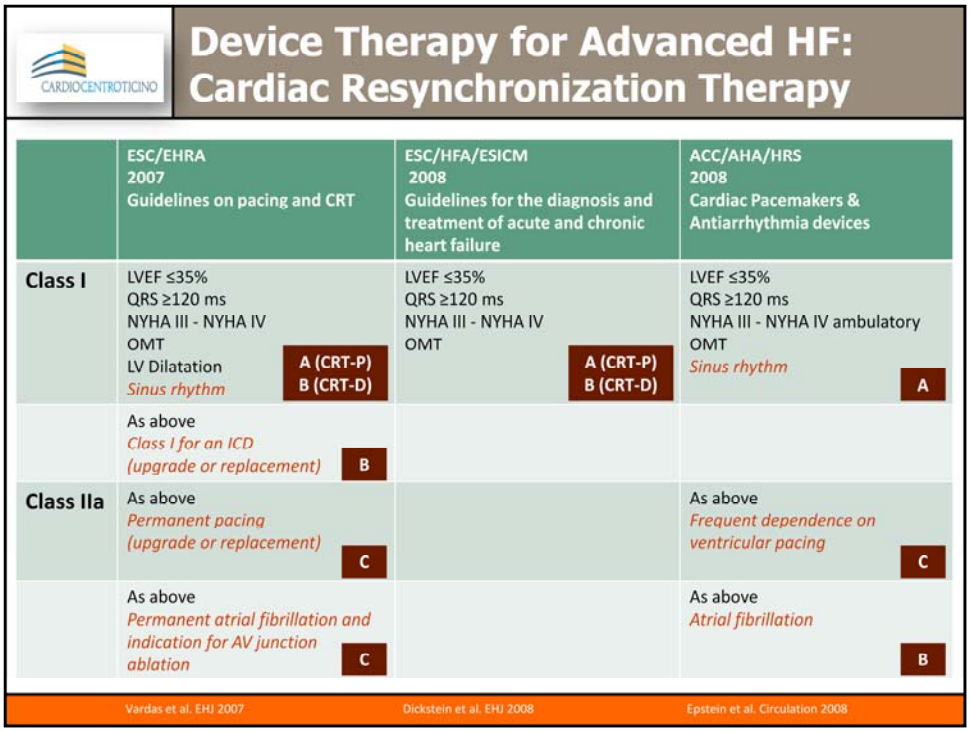
In the CARE-HF study this observation was confirmed by a post-hoc analysis. As shown in this slide, both diabetic and nondiabetic CRT patients had a similar frequency of death from any cause or unplanned hospitalization for a cardiovascular event of worsening heart failure.



Finally, interaction between renal failure and heart failure in CRT patients has received little attention so far. Most of the published data are pointing toward a worse prognosis of CRT patients with renal failure.



The importance of renal failure on top of presence of mechanical dyssychrony evaluated by magnetic resonance imaging and presence of posterolateral scar in CRT patients has been recently shown. Leyva et al. have created a multiparametric score which included several clinical and laboratory variables. These authors showed that only each of these 3 variables could significantly impact survival of CRT patients, the strongest one being location of a posterolateral scar. If this data will be confirmed in the future, it is very likely that our current indication to CRT will be amended. At the same time, the use of CRT in several new patient populations are currently evaluated and probably extension of the indication to functional class II patients is the new, upcoming indication.



Until that point, however we should continue to use and to consolidate currently available guidelines. As shown in my presentation, there is currently no contraindication to treat aged, multi-morbidity (diabetes, renal failure, etc.) by CRT. In rare circumstances however, it possible to diverge from these recommendations. This is a always a clinical decision which should be however shared with the patient and his/her family.