Cardiac Resynchronization Therapy: Benefits and Limitations in Heart Failure

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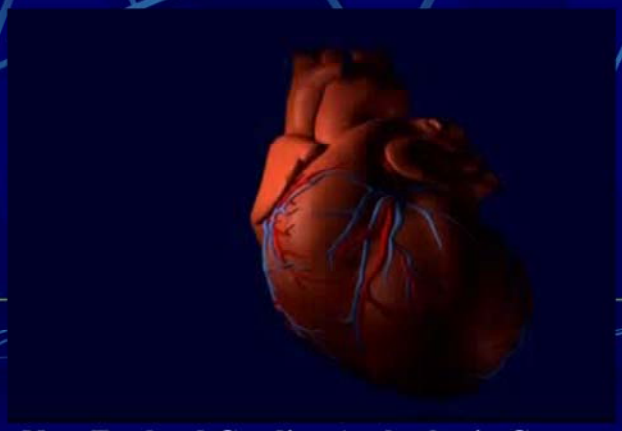
Cardiac Resynchronization Therapy (CRT)



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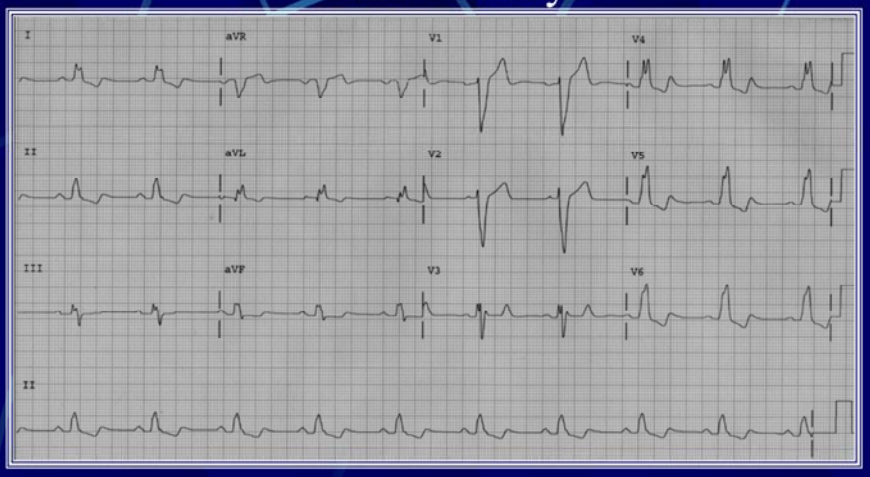
Cardiac Resynchronization Therapy (CRT)

- Up to 50% of patients with NYHA Class III-IV CHF have intra-ventricular conduction delays causing abnormal activation and contraction with subsequent intraventricular dyssynchrony
- Reduces systolic performance
- Mechanical inefficiency
- Worsened prognosis

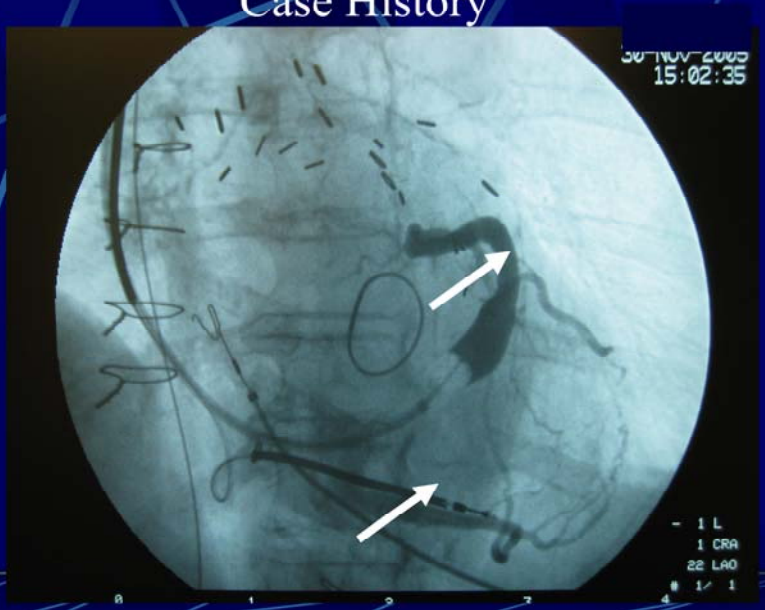
Limitations of CRT
Case History

- 62 year old male with progressive Class III CHF being evaluated for annual exam
- Prior CABG and MV repair
- LVEF 15% global hypokinesis
- Meds: BB, ACE, Diuretics, Statin, Aldactone
- PE: No orthostatic changes, S3 Gallop
- EKG: AF complete LBBB-QRS duration 140 ms
- HM: 4- 3 beats runs of NSVT, up to 240 PVCs/hr

Limitations of CRT
Case History



Limitations of CRT
Case History



Limitations of CRT
Case History

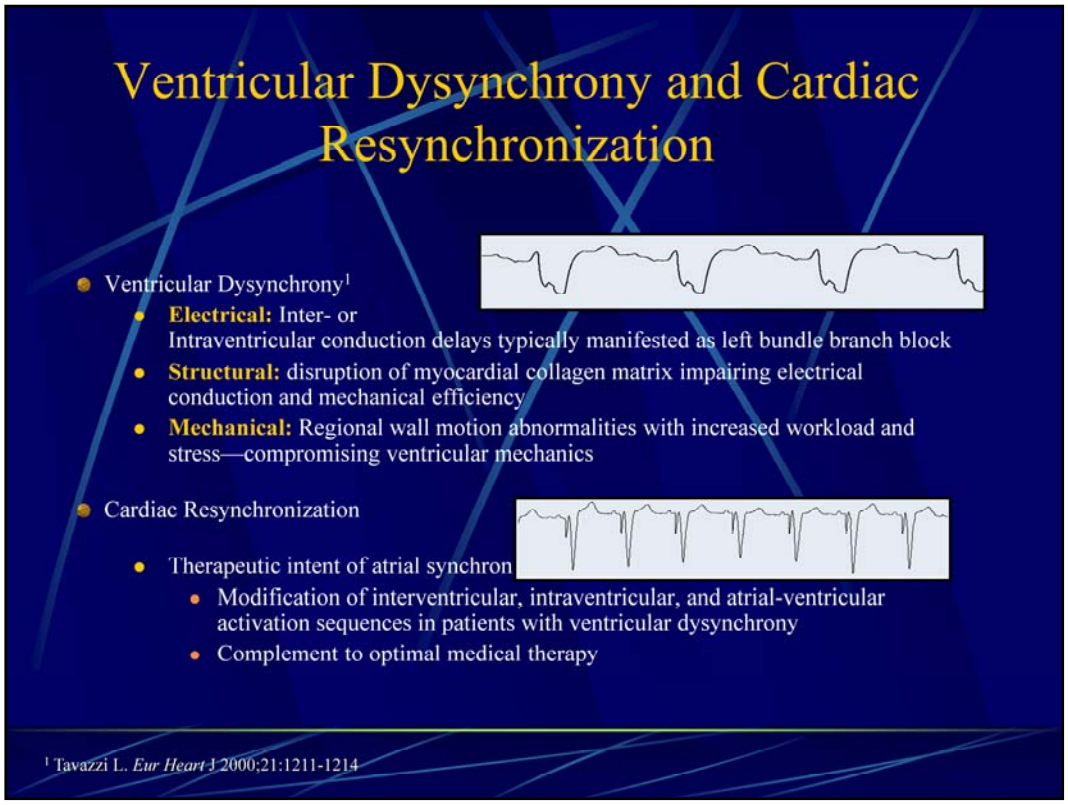
- Limited venous options at the time of LV lead placement
- LV lead placed in great cardiac vein R wave 3mv, threshold 3.2 V @ 0.5 ms
- AF rate difficult to control with BB and digoxin
- AV node ablated
- No clinical response despite AV and VV optimization
- Epicardial lead placed
- Clinical improvement in CHF symptoms

Current Criteria for CRT

- **Class IA**

  "Patients with LVEFs less than 35%, sinus rhythm, and NYHA class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than 120 ms, should receive CRT unless contraindicated."

ACC-AHA Heart Failure Guidelines (8/2005)



Introduces “new” terms used in this slide series.

Ventricular dysynchrony is defined as the effect caused by intra- and interventricular conduction defects or bundle branch block. Read Dr. Tavazzi’s editorial referenced here for a summary of the three potential causes of ventricular dysynchrony.

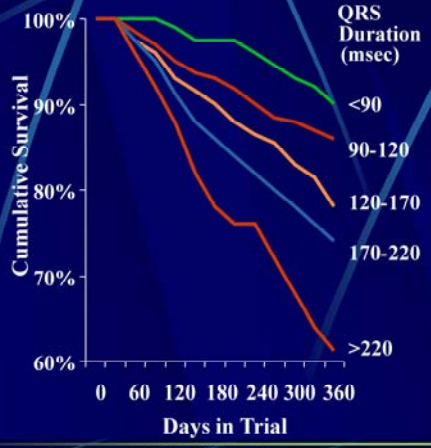
Cardiac resynchronization is defined as the therapeutic intent of atrial synchronized biventricular pacing for patients with heart failure and ventricular dysynchrony. The intent of the therapy is to resynchronize the ventricular activation sequence, and to better coordinate atrial-ventricular timing to improve pumping efficiency.

Cardiac resynchronization therapy is currently indicated for the reduction of symptoms of moderate to severe heart failure (NYHA Function Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction ≤ 35% and a QRS duration ≥130 ms. An ICD is also available for patients with a standard ICD indication who also meet the above listed criteria.

Using atrial-synchronized biventricular pacing in combination with optimal drug therapy has been shown to significantly improve a patient’s symptoms.

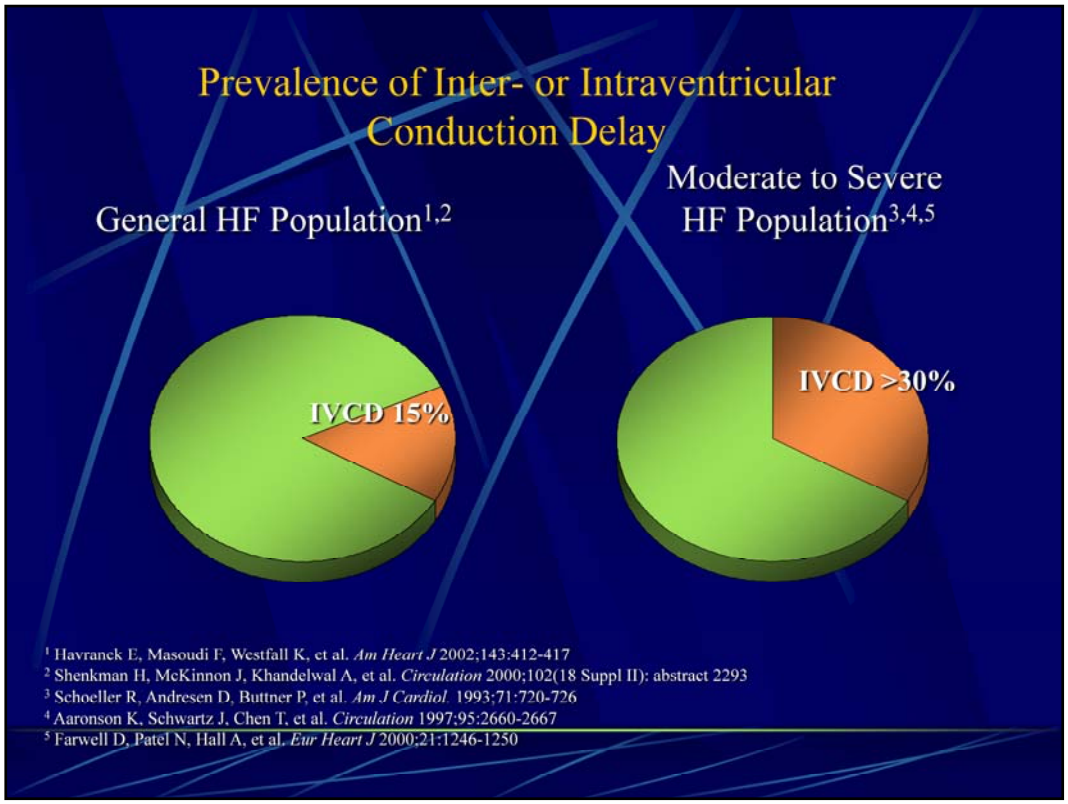
SCD in heart failure

QRS complex and mortality



- VEST study analysis
- NYHA class II-IV
- 3,654 ECGs
- QRS duration was found to be an independent predictor of mortality

Adapted from V Gottipaty, MD.



Approximately 15% of all heart failure patients have an inter- or intraventricular conduction delay (QRS > 120 msec)[1-2].

Over 30% of moderate to severe heart failure patients have a prolonged QRS. The prevalence of conduction defects increases with severity of heart failure.[3-5]

Shenkman and colleagues found the factors associated with prolonged QRS included: Older age, Male gender, Caucasian race, Lower EF, and Higher LVESD.

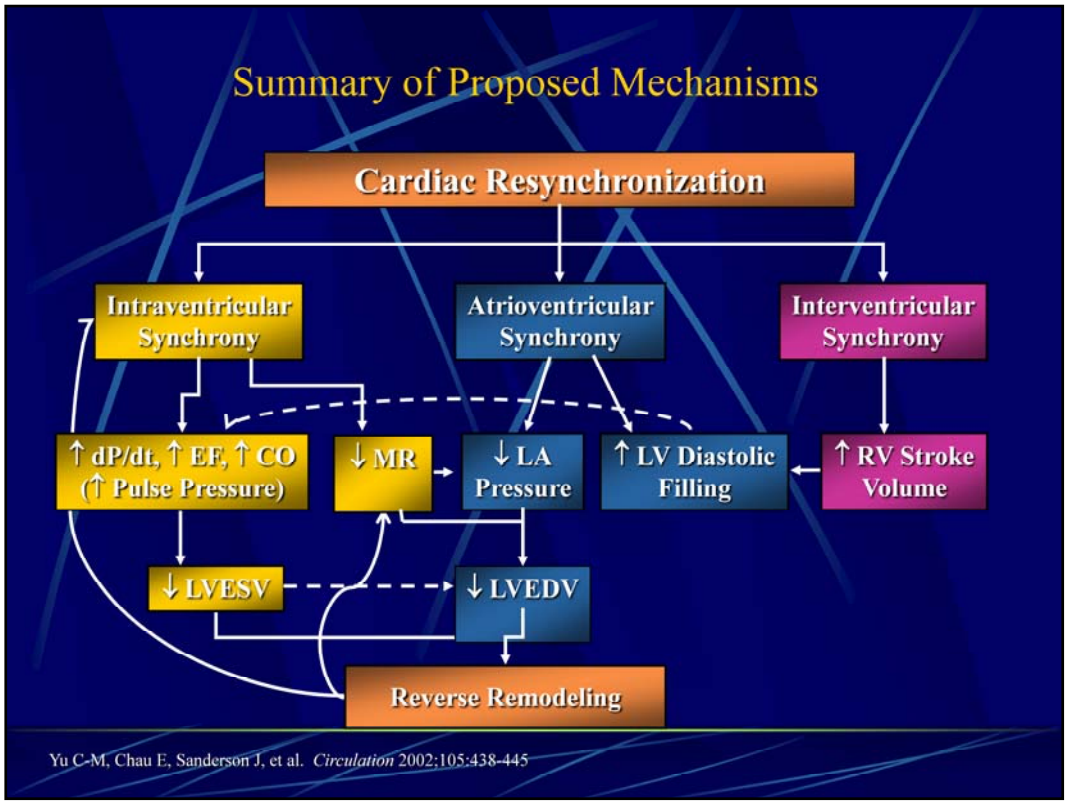
[1] Havranek EP, Masoudi FA, Westfall KA, Wolfe P, Ordin DL, Krumholz HM. Spectrum of heart failure in older patients: Results from the National Heart Failure Project. *Am Heart J* 2002;143:412-417.

[2] Shenkman HJ, McKinnon JE, Khandelwal AK, et al. Determinants of QRS Prolongation in a Generalized Heart Failure Population: Findings from the Conquest Study [Abstract 2993]. *Circulation* 2000;102(18 Suppl II).

[3] Schoeller R, Andresen D, Buttner P, Oezcelik K, Vey G, Schroder R. First-or second-degree atrioventricular block as a risk factor in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993;71:720-726.

[4] Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development & prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997; 95: 2660-2667.

[5] Farwell D, Patel NR, Hall A, Ralph S, Sulke AN. How many people with heart failure are appropriate for biventricular resynchronization? *Eur Heart J* 2000;21:1246-1250.



These paragraphs highlight some of the key findings from Yu's study (see slide reference).

Intraventricular synchrony

As a result of improved synchrony, systole becomes more effective and therefore, ejection fraction (EF), cardiac output (CO) and other parameters of cardiac function are improved. Left ventricular end-systolic volume (LVESV) is reduced. Mitral regurgitation (MR) attributable to distortion of the mitral apparatus is reduced by synchronizing the contractions and left atrial (LA) pressure is reduced. LV end-diastolic pressure and volume (LVEDV) are decreased.

Atrioventricular synchrony

A second mechanism is the shortening of the isovolumic contraction time (IVCT) after optimization of the atrioventricular delay. The effective diastolic filling time is increased, which in turn increases the stroke volume. In addition, LA pressure is reduced due to decreases in presystolic mitral regurgitation.

Interventricular synchrony

A less important mechanism is the improvement of interventricular synchrony between the right and left ventricles. This benefit may mediate through ventricular interdependence. This results in the gain in RV cardiac output, thereby augmenting the LV filling, resulting in overall improved cardiac function. The end effect of reverse remodeling will additionally improve cardiac synchrony and decrease secondary mitral regurgitation, forming a positive feedback loop.

Benefits are dependent upon pacing

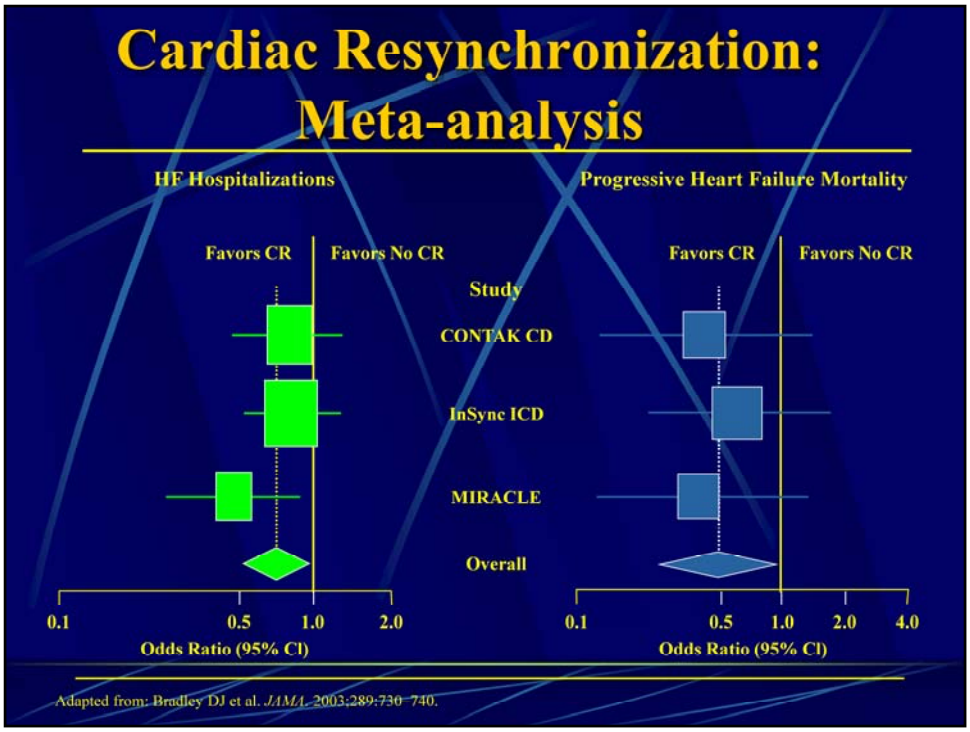
Withholding pacing resulted in loss of cardiac improvements. Improvement in diastolic filling time, isovolumic contraction time, and myocardial performance index (MPI) were lost immediately since they were largely dependent upon control of AV synchrony. Benefits on ejection fraction and cardiac output were lost over 4 weeks which suggest strongly that pacing is the cause of LV remodeling. Improvements in Quality of Life score and walking distance were maintained for at least 4 weeks after pacing was suspended. **These observations provide strong evidence that cardiac resynchronization therapy is the cause of LV reverse remodeling.**

CRT Trials

Trial (n)	Rand.	Blinded	QRS (ms)	EF%	NYHA Class	Results	Misc.
PATH-CHF (42)	Y	S	≥120		III-IV	+	no ICD
PATH-CHF II (89)	Y	S	120-150,>150	≤30	II-IV	+	
INSYNC (117)	N	N	≥150	<35	III-IV	+	no ICD
MUSTIC-SR (58)	Y	S	>150	<35	III	+	no ICD
MUSTIC-AF (43)	Y	S	>200*	<35	III	+	no ICD
MIRACLE (453)	Y	D	≥130	≤35	III-IV	+	no ICD
MIRACLE ICD (369)	Y	D	≥130	≤35	III-IV		
CONTAK CD (490)	Y	D	≥120	≤35	II-IV	+	
COMPANION (1520)	Y	N	≥120	≤35	III-IV	+	± ICD
CARE HF (800)	Y	N	120-150,>150	<35	III-IV	+	120-150 TDI

* RV paced QRS ¶ Primary endpoint not met; key secondary endpoints reached

Cardiac Resynchronization: Meta-analysis



Adapted from: Bradley DJ et al. *JAMA*. 2003;289:730–740.

Bi-ventricular Resynchronization

Characteristics of Patients in Whom CRT is Strongly Supported by Randomized Trails

- Sinus Rhythm
- LVEF < 35%
- QRS duration >130 ms
- Ischemic or nonischemic cardiomyopathy
- NYHA Functional class III or IV
- Maximal pharmacologic therapy for heart failure

Gregoratos et al Circulation 2002;106:22145-2161
Adams et al J Cardiac Failure 2006;12;10-38
Hunt et al Circulation. 2005;112;e154-e235
Strickberger et al Circulation. 2005;111:2146-215

Bi-ventricular Resynchronization

Bi-ventricular Resynchronization

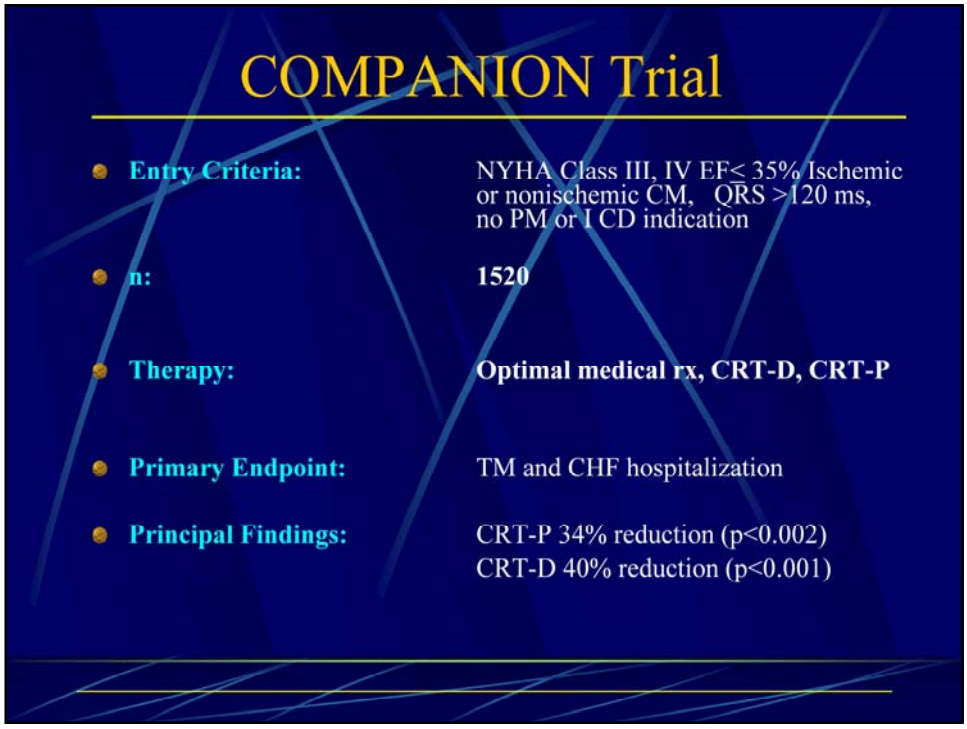
- Class I/IIA
  - Class III HF, Ambulatory Class IV HF, LVEF <35%
    with LV dilatation > 5.5 cm, QRS ≥120 ms
    CAD, NICM-COMPANION
- Class III
  - Class IV CHF with no reasonable expectation for improvement

Gregoratos et al Circulation 2002;106:22145-2161
Adams et al J Cardiac Failure 2006;12;10-38
Hunt et al Circulation. 2005;112:e154-e235
Strickberger et al Circulation. 2005;111:2146-215

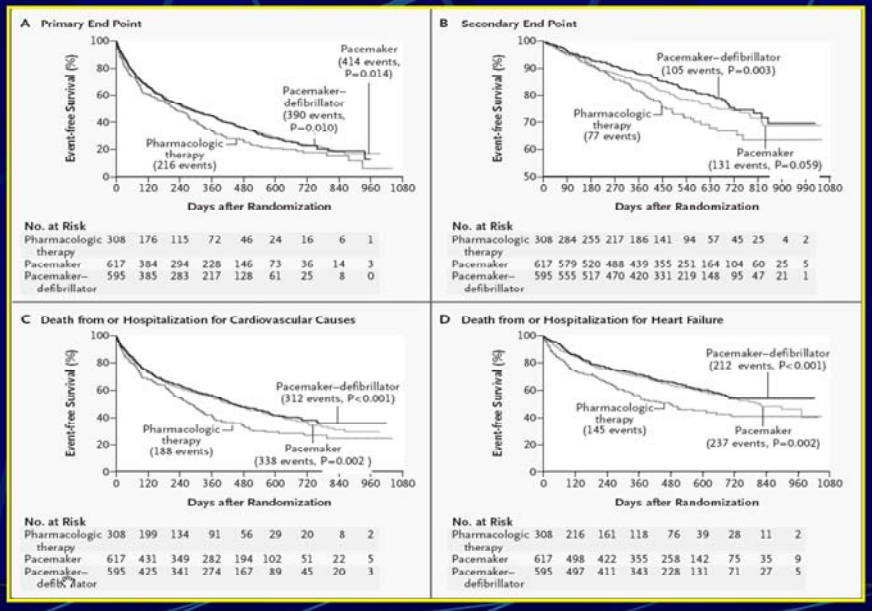
Bi-ventricular Resynchronization

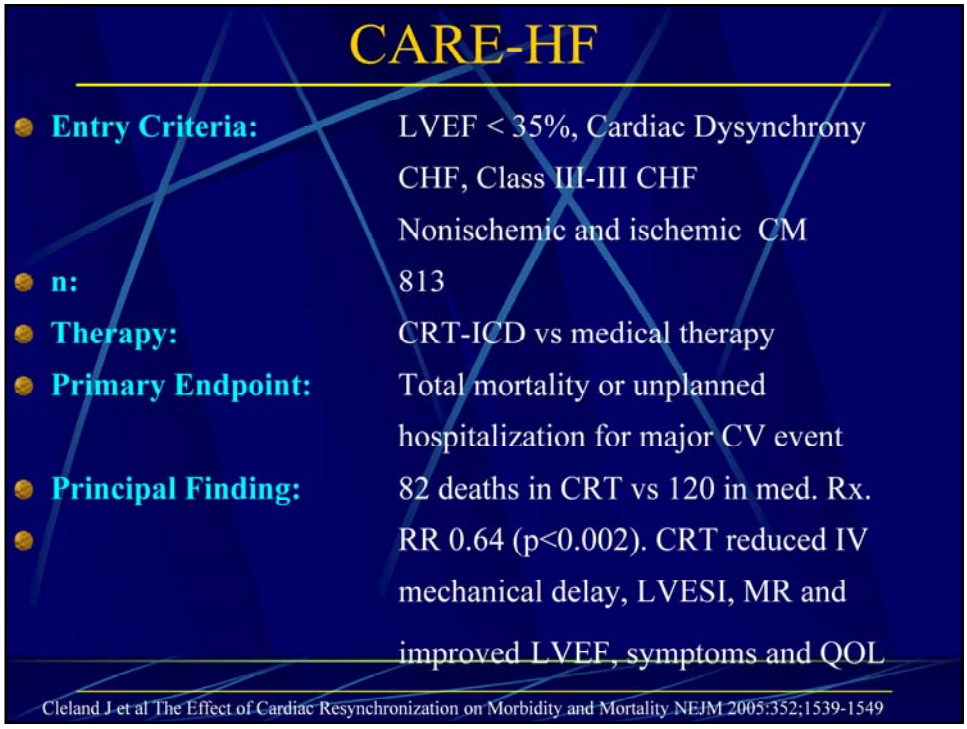
- Recently, 2 randomized multicenter trials assessed the benefit of CRT in patients with NYHA functional class II, depressed LVEF, a wide QRS duration, and an indication for implantable defibrillator therapy.
- CRT demonstrated functional improvement as well as left ventricular remodeling.
- At present the use of CRT in patients with minimal heart failure symptoms is not recommended and is the focus of ongoing clinical trials.

Strickberger et al Circulation. 2005;111:2146-215 Higgins SL, et al J Am Coll Cardiol. 2003;42:1454 –1459
Abraham WT Circulation. 2004;110: 2864 –2868

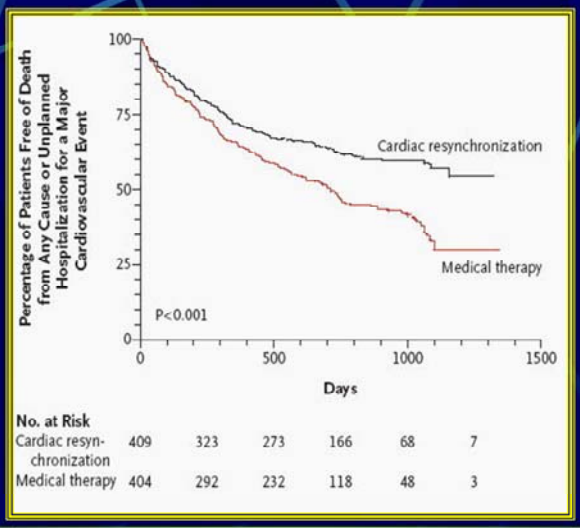

COMPANION Trial
Entry Criteria:
NYHA Class III, IV EF≤ 35% Ischemic or nonischemic CM, QRS >120 ms, no PM or I CD indication
n:
1520
Therapy:
Optimal medical rx, CRT-D, CRT-P
Primary Endpoint:
TM and CHF hospitalization
Principal Findings:
CRT-P 34% reduction (p<0.002)
CRT-D 40% reduction (p<0.001)

COMPANION Trial



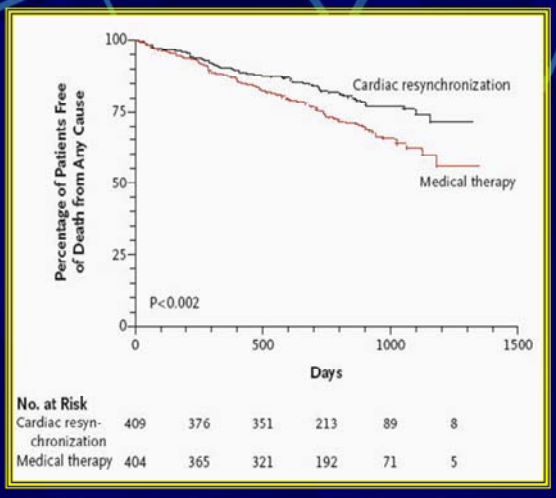

CARE-HF
Entry Criteria:
LVEF < 35%, Cardiac Dysynchrony
CHF, Class III-III CHF
Nonischemic and ischemic CM
n:
813
Therapy:
CRT-ICD vs medical therapy
Primary Endpoint:
Total mortality or unplanned
hospitalization for major CV event
Principal Finding:
82 deaths in CRT vs 120 in med. Rx.
RR 0.64 (p<0.002). CRT reduced IV
mechanical delay, LVESI, MR and
improved LVEF, symptoms and QOL
Cleland J et al The Effect of Cardiac Resynchronization on Morbidity and Mortality NEJM 2005:352;1539-1549

CARE-HF



Cleland J et al The Effect of Cardiac Resynchronization on Morbidity and Mortality NEJM 2005:352;1539-1549

CARE-HF

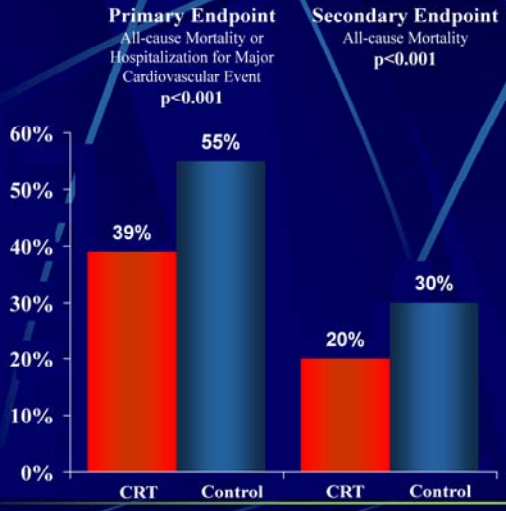


No. at Risk						
Cardiac resynchronization	409	376	351	213	89	8
Medical therapy	404	365	321	192	71	5

Cleland J et al The Effect of Cardiac Resynchronization on Morbidity and Mortality NEJM 2005:352;1539-1549

CARDIAC RESYNCRONIZATION THERAPY

CARE HF



- Baseline clinical characteristics were similar between the treatment groups, with 46% of patients having non-ischemic dilated cardiomyopathy and 38% with ischemic heart disease.
- Mean LV ejection fraction was 25%.
- Of the 409 patients randomized to the CRT device, 95% had a successful implantation.
- The primary endpoint of all-cause mortality

CRT and Atrial Fibrillation

- CRT does not prevent or increase the induction of atrial fibrillation
- One randomized study shows benefit of CRT on heart failure indices in pts with chronic AF
- Biventricular capture may be inadequate in pts with poorly controlled ventricular response
- Benefits of CRT may only be extended to chronic AF patients with previous AV junctional ablation

CRT Non-responders

- Retrospective analysis of Miracle Study looking for at clinical variables
- Dominant R wave in lead AVR, RBBB, and evidence of prior anterior wall MI were all associated with smaller improvements with delta VO2 measurements
- ECG markers of anterior wall MI and RV dilatation may identify pts unlikely to benefit from biventricular pacing

Reynolds et al.Relationship of baseline electrocardiographic characteristics with the response to cardiac resynchronization therapy for heart failure. Pacing & Clinical Electrophysiology. 27(11):1513-8, 2004 Nov.

ICD and Bi-ventricular Resynchronization-Risks

The risks associated with the implantation of a CRT device are relatively small and are similar to the risks and complications associated with the transvenous implantation of a permanent pacemaker or implantable defibrillator.

ICD and CRT

Complication	Frequency
Bleeding	1%
Pheumothorax	1%
Pericardial Effusion without tamponnade	1%
MI	.02%
Stroke	.02%
Death	.02%

CRT

CS dissection	1%
Lead dislodgement	5%
Phrenic stimulation	5%
Renal dysfunction	1%

Cazeau S, et al *N Engl J Med.* 2001;344:873– 880.
Auricchio A, et al *J Am Coll Cardiol.* 2002;39:2026 –2033.
Abraham WT et al *N Engl J Med.* 2002;346:1845–1853.
Young JB et al *JAMA.* 2003;289:2685–2694.
Higgins SL, et al *J Am Coll Cardiol.* 2003;42:1454 –1459.
Bristow MR et al. *N Engl J Med.* 2004;350:2140 –2150.

What if the patient does not respond?

- In those rare patients who do not respond, we have the ability to optimize the timing of contraction of the various chamers in the heart (A to V, V to V) with advanced imaging techniques that allow those small group of nonresponders to also improve.

- We should be mindful that all of these patients get the benefit of CRT, plus protection against symptoms from slow heart rhythms and protection against life threatening arrhythmias coming from the ventricle which would otherwise result in sudden cardiac arrest

Limitations of CRT Therapy

- Absence of robust data in those with AF
- Absence of robust data in those with RBBB
- Absence of survival benefit in Class IV patinets
- Inability to cannulate the CS
- Absence of adequate venous anatomy
- Complications
- Cost
- Time and effort of AV and VV synchronization
- Nonresponders despite optimization