Cardiac Resynchronisation Therapy

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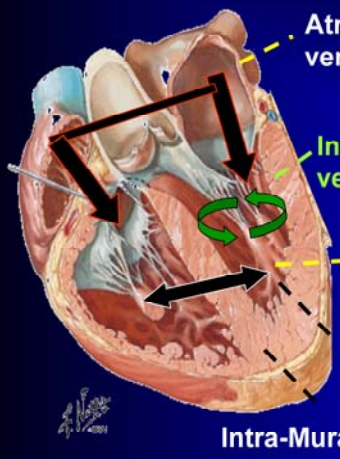
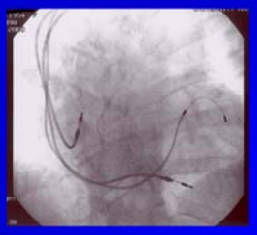
Cardiac Dyssynchrony





What do we Know About Dyssynchrony / CRT?

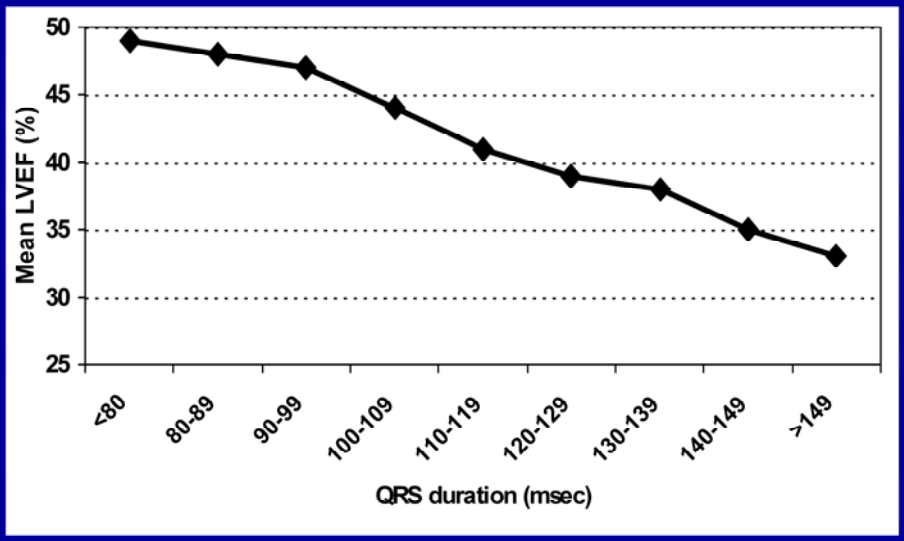
What We Know

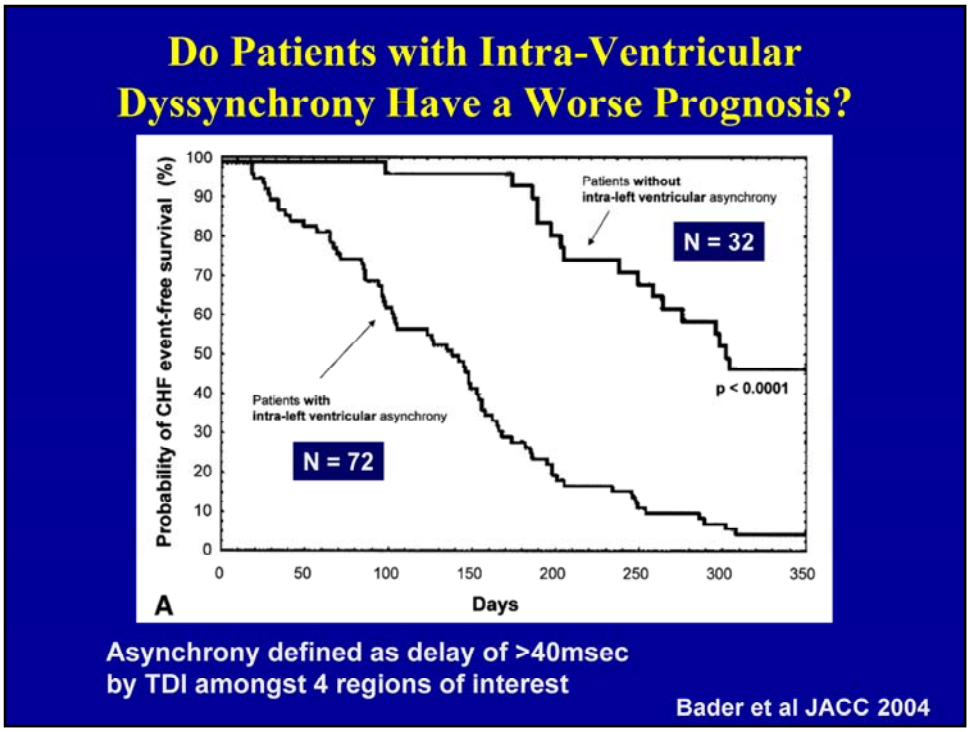
- Broad QRS is associated with a worse prognosis
- CRT is effective if
  - LVSD and dilatation
  - NYHA III/IV
  - QRS >120msec

What We Don't Know

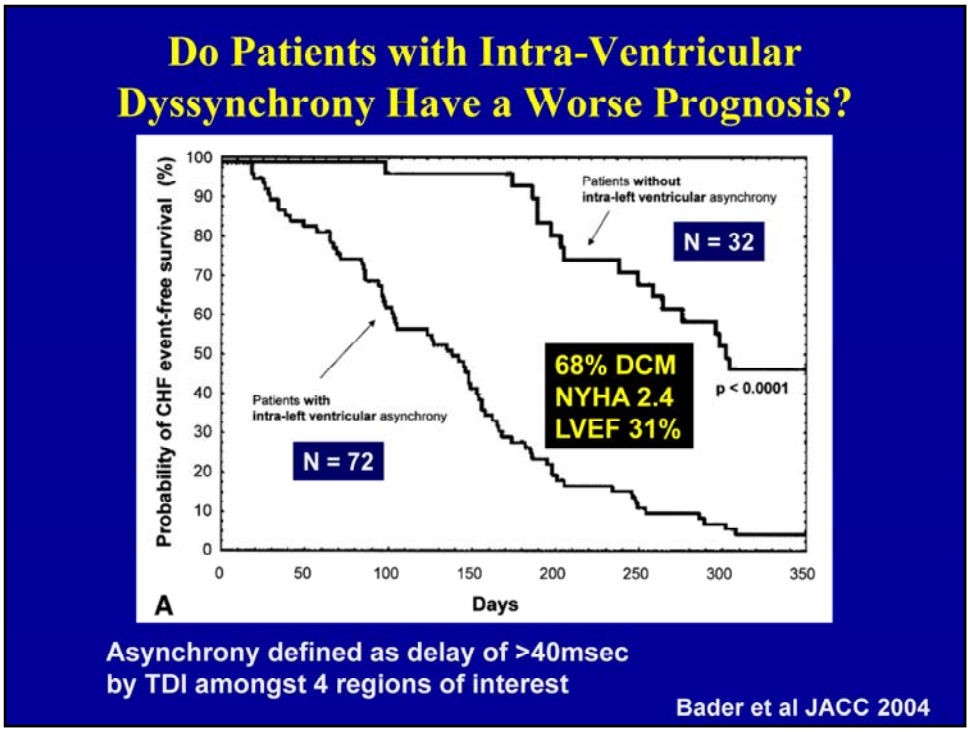
- Dyssynchrony is associated with a poor prognosis
- CRT is ineffective if
  - LVSD/dilatation is absent
  - NYHA I/II
  - QRS <120msec
- Dyssynchrony
  - Can be readily measured
  - Is the substrate for CRT

Relationship between QRS and LVEF (EuroHeart Failure Survey N = 5,934)





There is remarkably little evidence that echocardiographic dyssynchrony is associated with a worse prognosis and some evidence that it may be associated with a better one. This is the only study to suggest a worse outcome with dyssynchrony. It was a small study. The outcome investigated was death or heart failure hospitalisation. The event rates were exceedingly high for patients with predominantly NYHA class II heart failure due to dilated cardiomyopathy and with a relatively good LVEF. This effect may have occurred by chance.



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Trials of CRT v Control

- MUSTIC-SR
- MUSTIC-AF
- CONTAK
- MIRACLE
- MIRACLE-ICD
- MIRACLE-ICD-II
- PAVE (AF)
- COMPANION
- CARE-HF

Summary of Results

- **Reduction in mortality**
  - SCD and WHF by about half
  - All-cause mortality by one third
  - 4-5 lives saved/ 100 device-yrs
- **Improvement in**
  - cardiac function
  - Symptoms
  - HF hospitalisation
- **Platform for other devices**
  - ATP, monitoring
- **Modest initial cost**
- **Adverse effects**
  - Procedure
  - Not all patients benefit (?)

CARE-HF
Main Inclusion & Exclusion Criteria

- Heart failure for ≥6 wks treated with loop diuretics
- In NYHA class III/IV at time of enrolment
- A high standard of pharmacological therapy

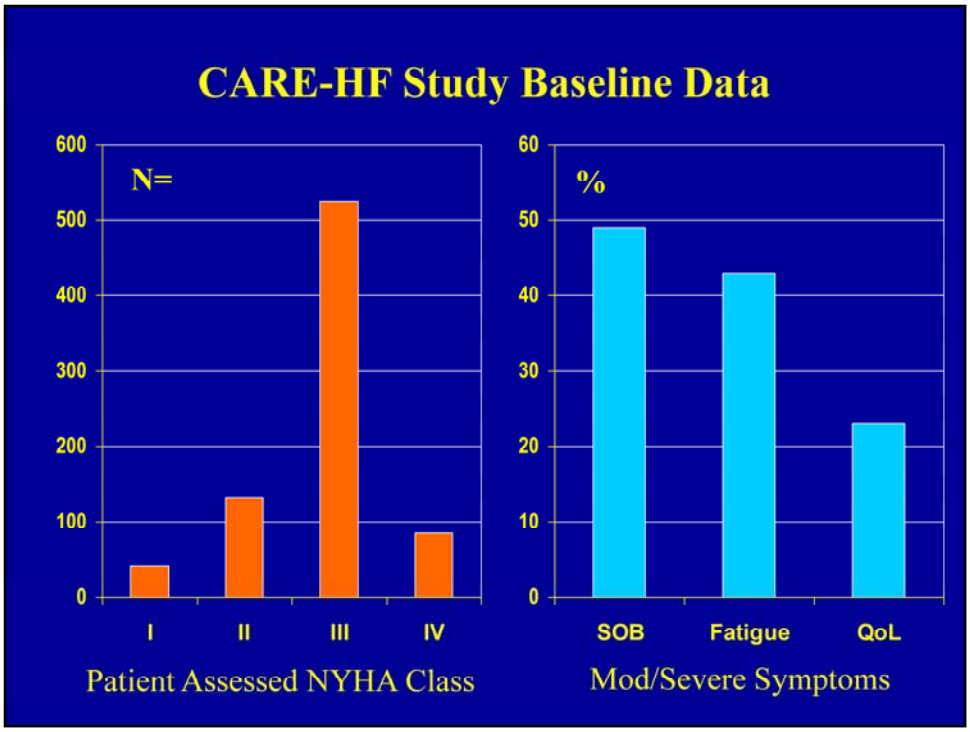
- LV systolic dysfunction and dilation
  - EF ≤35%; EDD >30mm/height in metres

- QRS ≥120 ms
  - And echo dyssynchrony if QRS 120-149 ms
    - **Interventricular mechanical delay >40 ms**

- Patients with AF or requiring pacing excluded

Baseline Characteristics (1)

	Control n = 404	CRT n = 409
Age [yr] - median (IQR)	66 (59 to 72)	67 (60 to 73)
Male (%)	293 (73%)	304 (74%)
NYHA IV (%)	27 (6.7%)	23 (5.6%)
Ischaemic heart disease (%)	142 (35%)	167 (41%)
Treatment (%)		
ACEIs / ARBs	383 (95%)	387 (95%)
Beta blockers	298 (73%)	288 (71%)
Furosemide Eq ≥ 80 mg/day	177 (44%)	175 (43%)
Digitalis	181 (45%)	165 (40%)
Spironolactone	238 (59%)	219 (54%)


CARE-HF Study Baseline Data
N=
600
500
400
300
200
100
0
I
II
III
IV
Patient Assessed NYHA Class
%
60
50
40
30
20
10
0
SOB
Fatigue
QoL
Mod/Severe Symptoms

Baseline Characteristics (2)

Parameter (median [IQR])	Control n = 404	CRT n = 409
Heart rate [bpm]	**70 (61 to 78)**	**69 (60 to 78)**
Systolic BP [mm Hg]	**110 (100 to 125)**	**110 (100 to 125)**
Diastolic BP [mm Hg]	**70 (60 to 80)**	**70 (60 to 79)**
QRS interval [ms]	**160 (152 to 180)**	**160 (152 to 180)**
IVMD [ms]	**50 (30 to 66)**	**49 (32 to 67)**
Ejection fraction	**25 (22 to 29)**	**25 (21 to 29)**
ESV index (ml/m^2)	**117 (94 to 147)**	**121 (92 to 151)**
MR area [cm^2]	**23 (11 to 34)**	**21 (12 to 33)**
GFR [mL min^{-1}]	**61 (46 to 73)**	**60 (46 to 73)**
NT proBNP [pg mL^{-1}]	**1,806 (719 to 3,949)**	**1,920 (744 to 4,288)**

Mechanistic Outcomes

Care - HF

Outcome	Mean difference	
	at 3 mth*	at 18 mth*
Systolic BP (mm Hg)	**+5.8 (P < 0.0001)**	**+6.3 (P < 0.0001)**
Interventricular mechanical delay (ms)	**-21 (P < 0.0001)**	**-21 (P < 0.0001)**
Ejection fraction (%)	**+3.7 (P < 0.0001)**	**+6.9 (P < 0.0001)**
Left ventricular end-systolic volume (ml/m^2)	**-18.2 (P < 0.0001)**	**-26.0 (P < 0.0001)**
MR [% of LA area]	**-5.1 (P < 0.0001)**	**-4.2 (P = 0.003)**
NT Pro-BNP [$pg\ mL^{-1}$]	**-225 (P = 0.36)**	**-1,122 (P = 0.0016)**

* Positive values indicate higher value with CRT compared to control

cr1

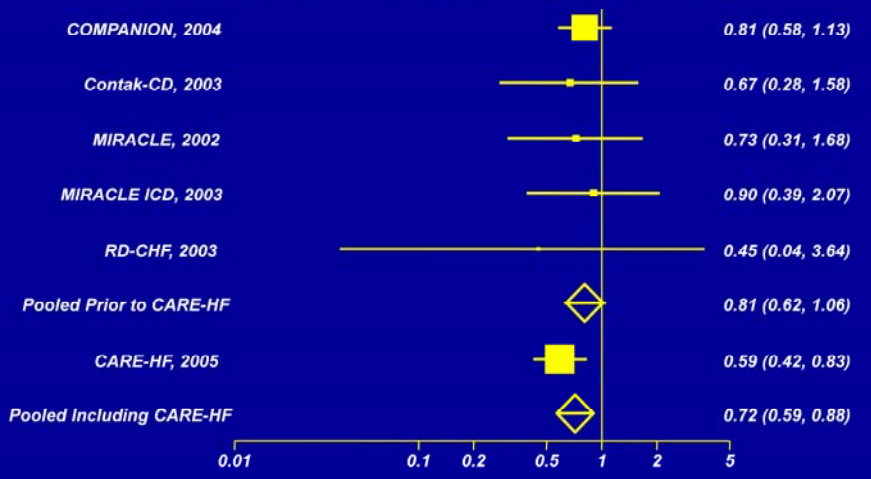
Results of Main Study

	Medical Therapy	CRT	Hazard/ Odds Ratio	P value
Primary EP	**224 (55%)**	**159 (39%)**	**0.63* (0.51- 0.77)**	**<0.001**
Mortality	**120 (30%)**	**82 (20%)**	**0.64 (0.48 - 0.85)**	**=0.002**
Death or HF Hosp	**191 (47%)**	**118 (29%)**	**0.54 (0.43 - 0.68)**	**<0.001**
NYHA I/II at 90 Days	**144[#] (40%)**	**270[#] (71%)**	**4.1 (2.9 - 5.8)**	**<0.001**

*Consistent effect across subgroups including IHD/non-IHD

[#]Patients (n and %) alive in whom NYHA reported

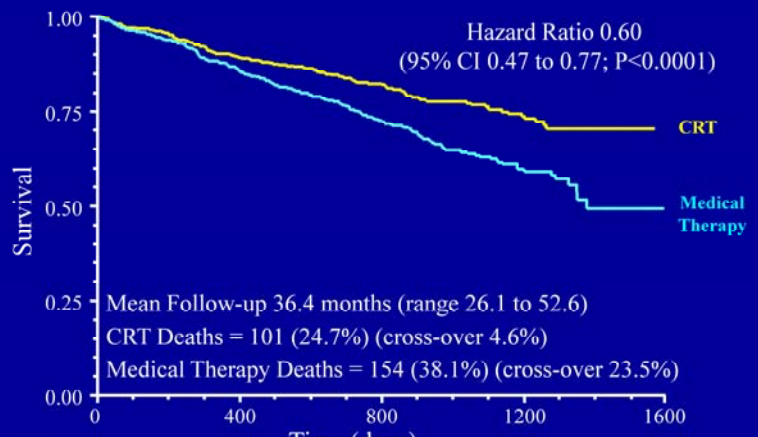
Effect of CRT on Mortality
Odds Ratio & 95% Confidence Intervals



Not including CARE-HF extension data
Freemantle N et al Eur J Heart Failure 2006

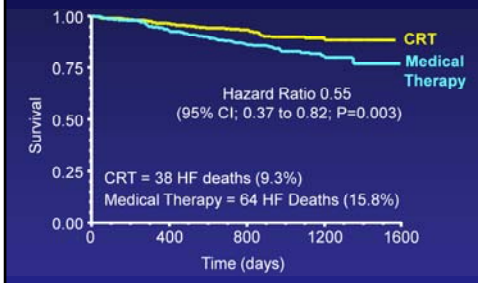
Care - HF

CARE-HF Extension Study
Effect of CRT on All-Cause Mortality

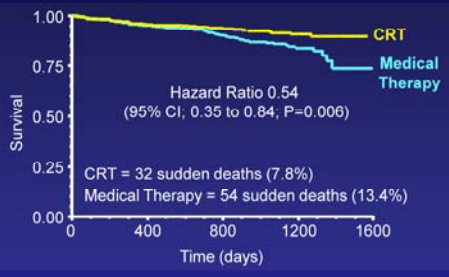


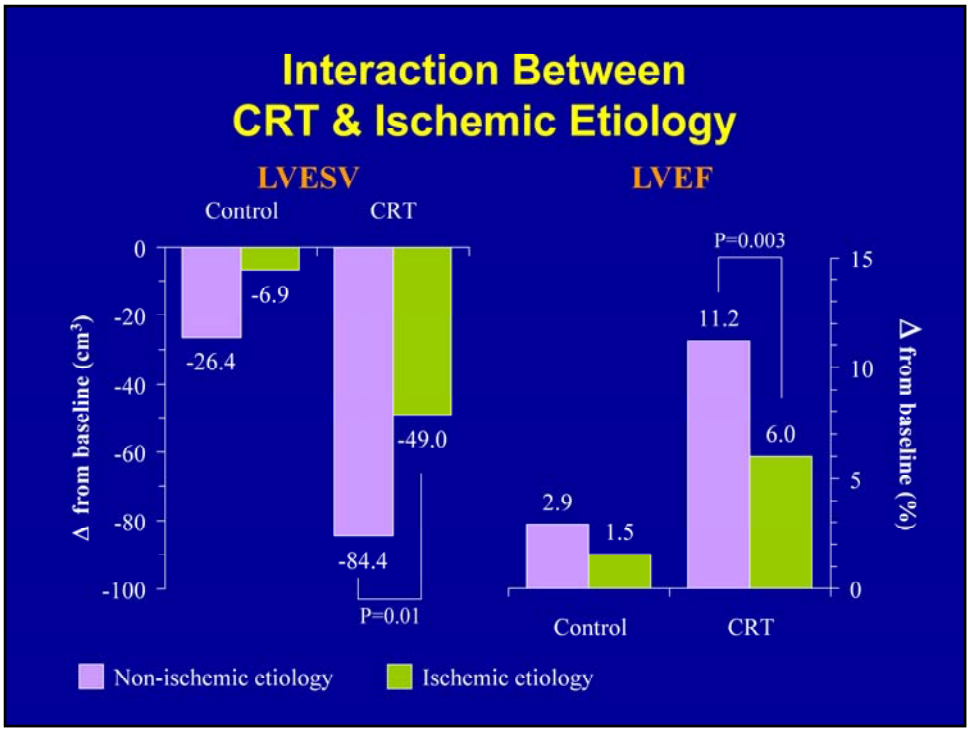
Number at risk							
CRT	409	383	358	338	209	85	9
Medical therapy	404	372	331	298	178	63	6

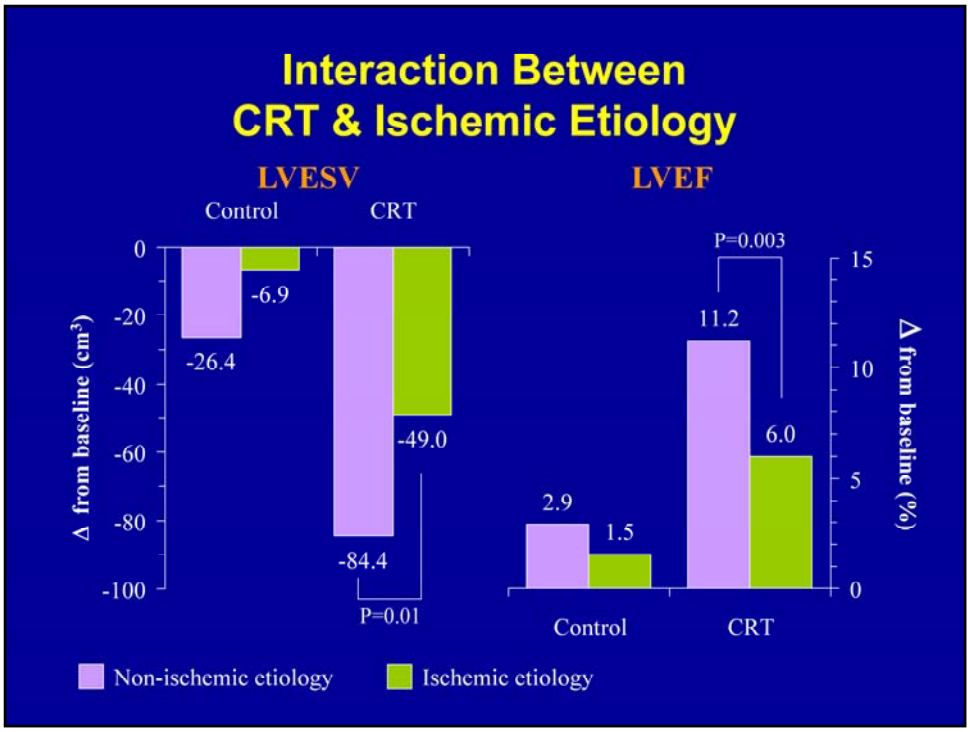
CARE-HF Extension Study
Time to Death From Worsening Heart Failure



CARE-HF Extension Study
Time to Sudden Cardiac Death




Interaction Between
CRT & Ischemic Etiology
LVESV
LVEF
Control
CRT
Δ from baseline (cm³)
0
-20
-40
-60
-80
-100
-26.4
-6.9
-84.4
-49.0
P=0.01
P=0.003
2.9
1.5
11.2
6.0
15
10
5
0
Δ from baseline (%)
Control
CRT
Non-ischemic etiology
Ischemic etiology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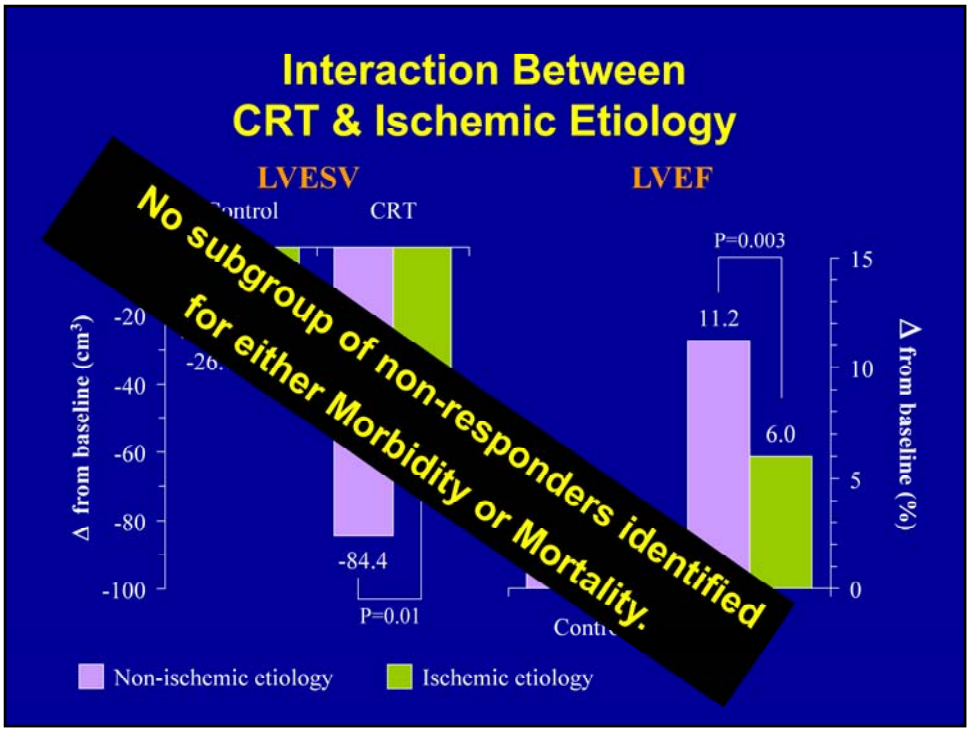
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LVESV
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P=0.003
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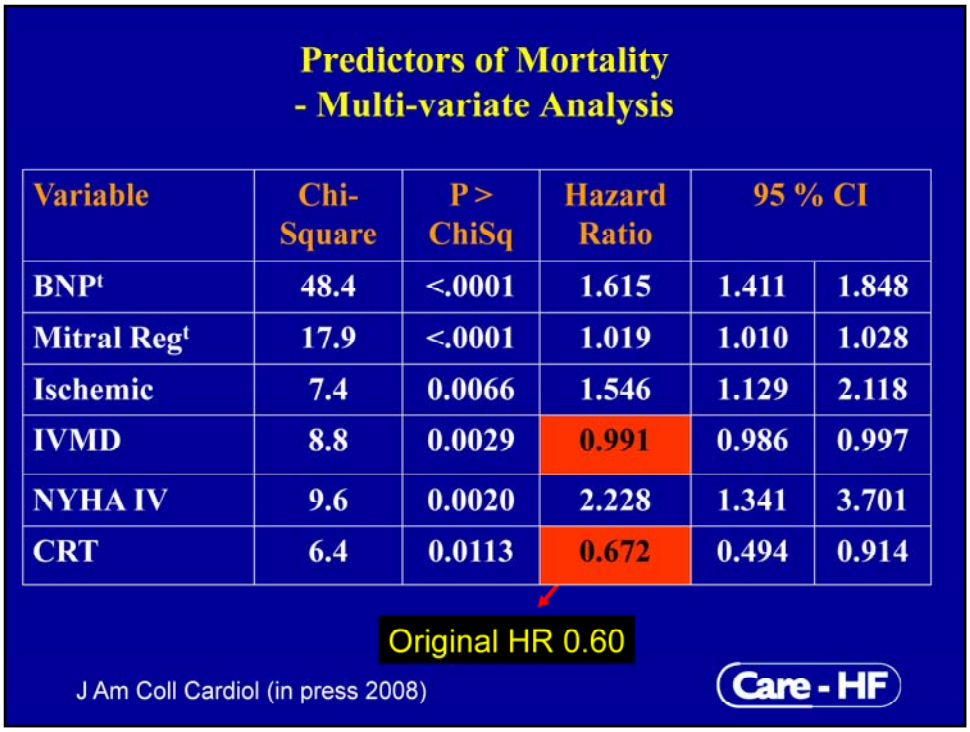
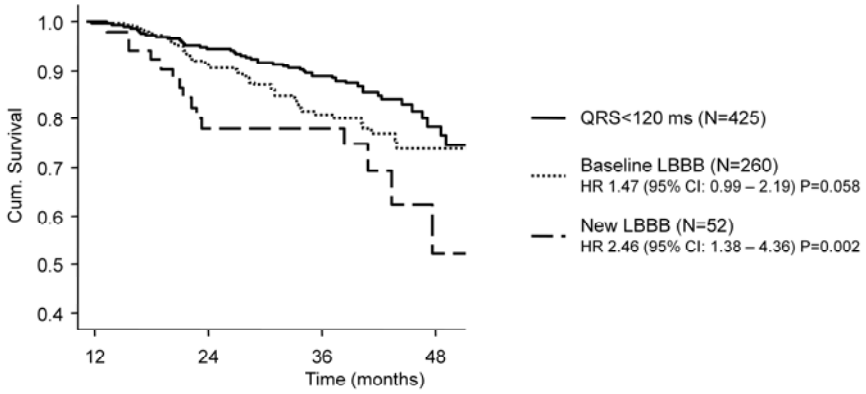
6.0
5
-20
-40
-60
-80
-100
0
Δ from baseline (cm³)
Δ from baseline (%)
-84.4
P=0.01
Non-ischemic etiology
Ischemic etiology
No subgroup of non-responders identified
for either Morbidity or Mortality.



Patients with greater IVMD had a better prognosis. Other variables measured at baseline and at 3 months (and therefore accounting for the early effects of CRT on cardiac function) accounted for little of the long-term effect of CRT on mortality.

When to Measure Dyssynchrony?

Kingston-upon-Hull Heart Failure Clinic



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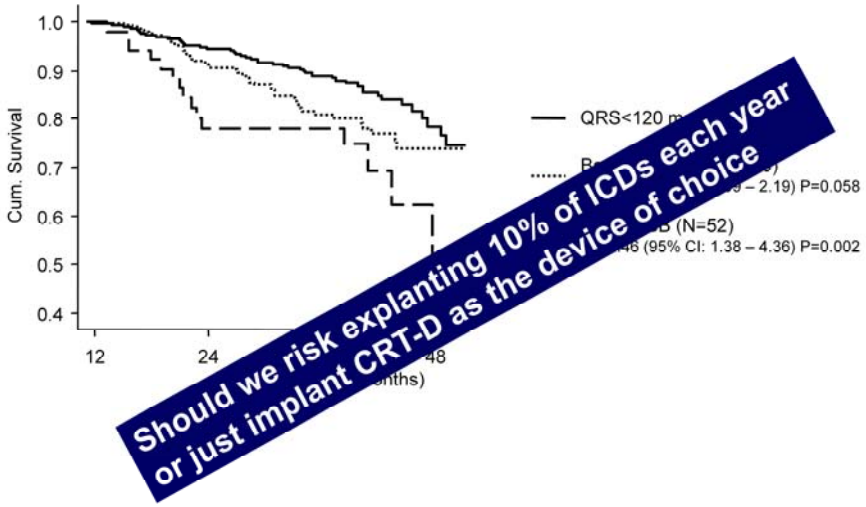
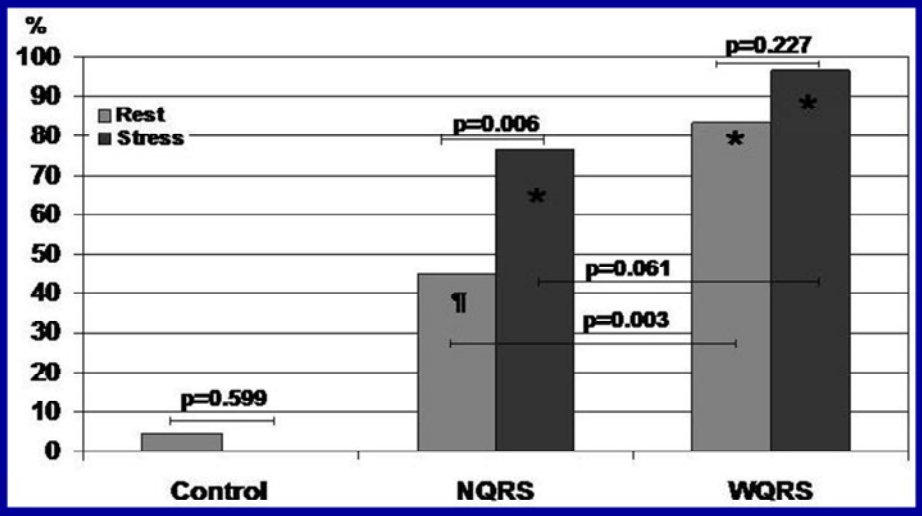


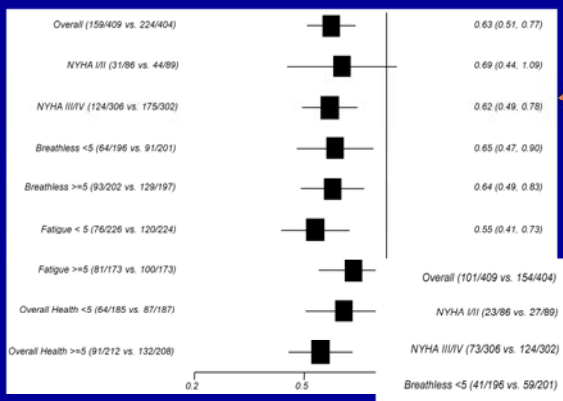
Should we risk explanting 10% of ICDs each year or just implant CRT-D as the device of choice

When to Measure Dyssynchrony?



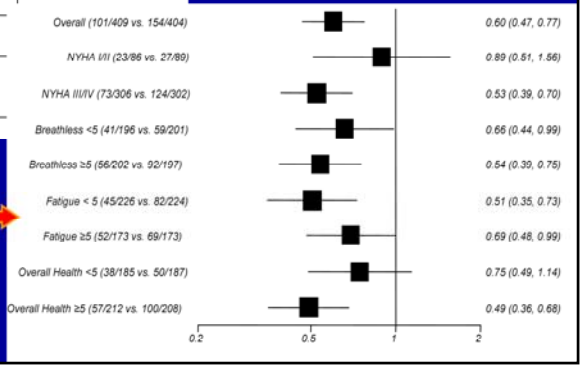
Chattopadhayay Eur J Heart Failure 2008

Should Symptoms Guide Use of CRT?



Primary Outcome

All-Cause Mortality



Who Should Have CRT?

To improve symptoms consider patients with

- persistent or relapsing NYHA III/IV symptoms
- dilated LV and grossly reduced LVEF
- (With QRS $\geq$120msec ?)
- No evidence that we know how to identify responders

To improve prognosis

- CRT is indicated as above but regardless of symptoms
- No evidence that we know how to identify responders

To 'future' proof

- CRT is indicated in all patients with LVSD who require a pacemaker or ICD

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Scar Burden?

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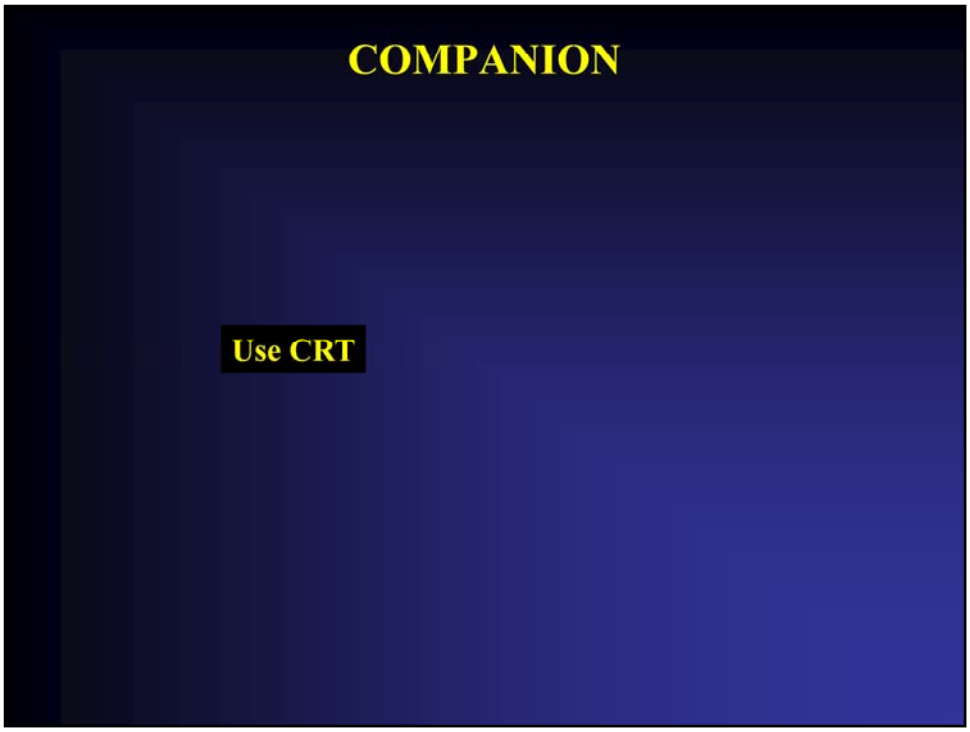
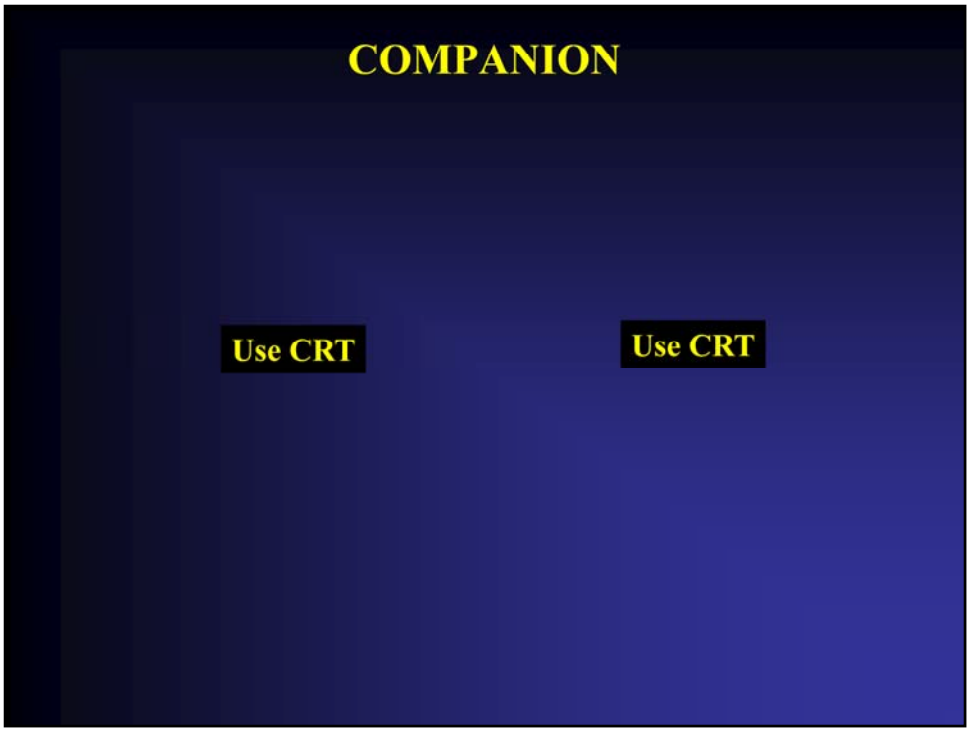
COMPANION


COMPANION
Use CRT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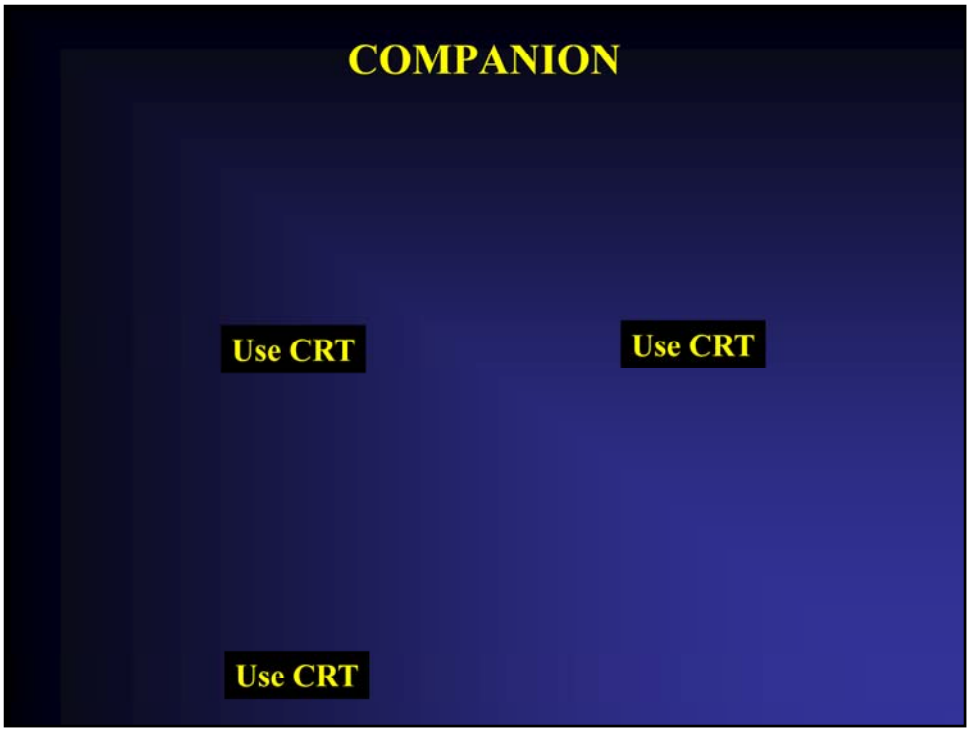
Use CRT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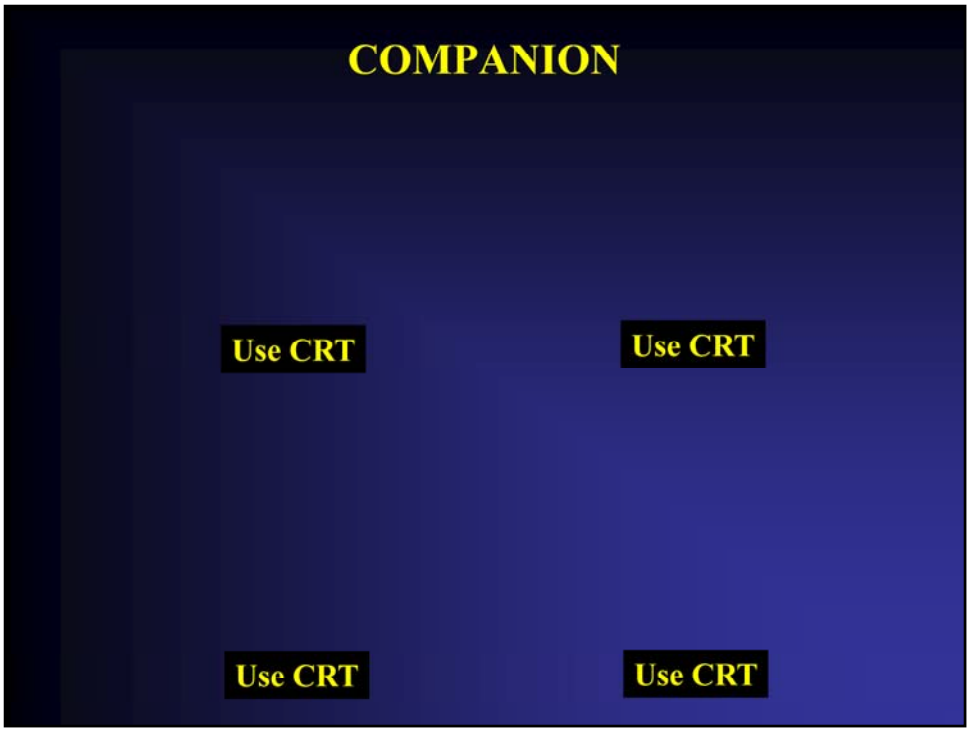
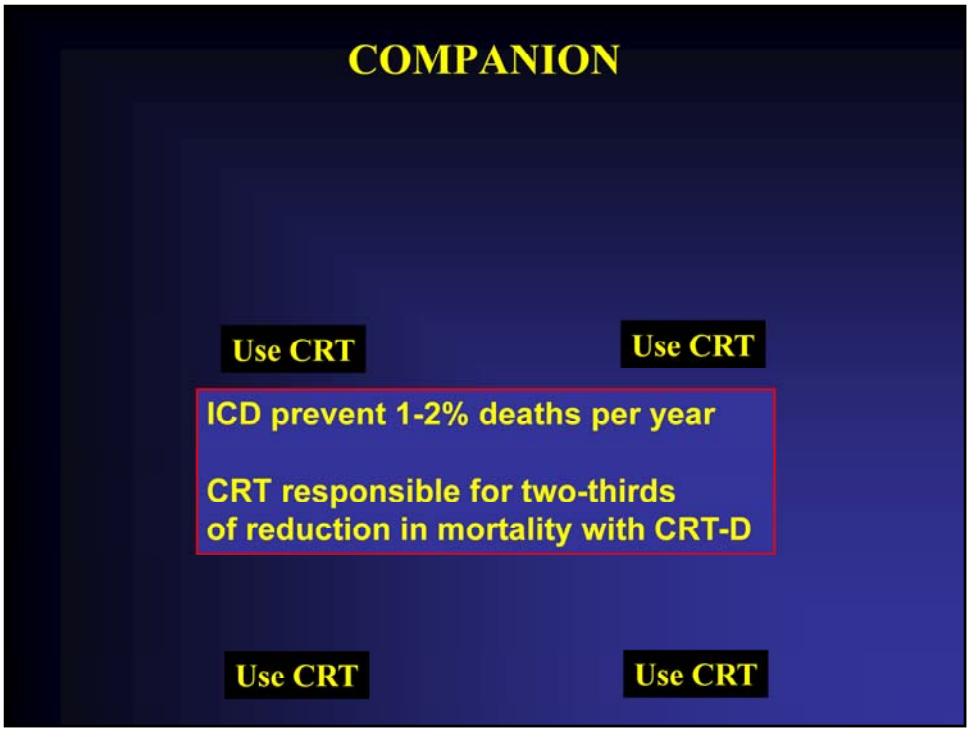
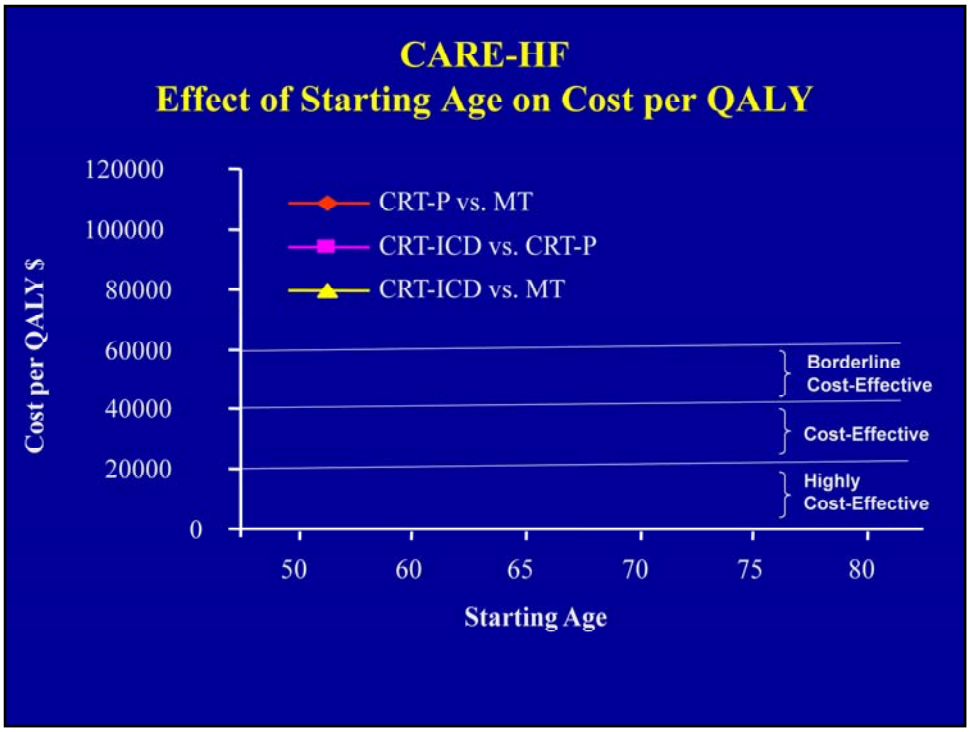
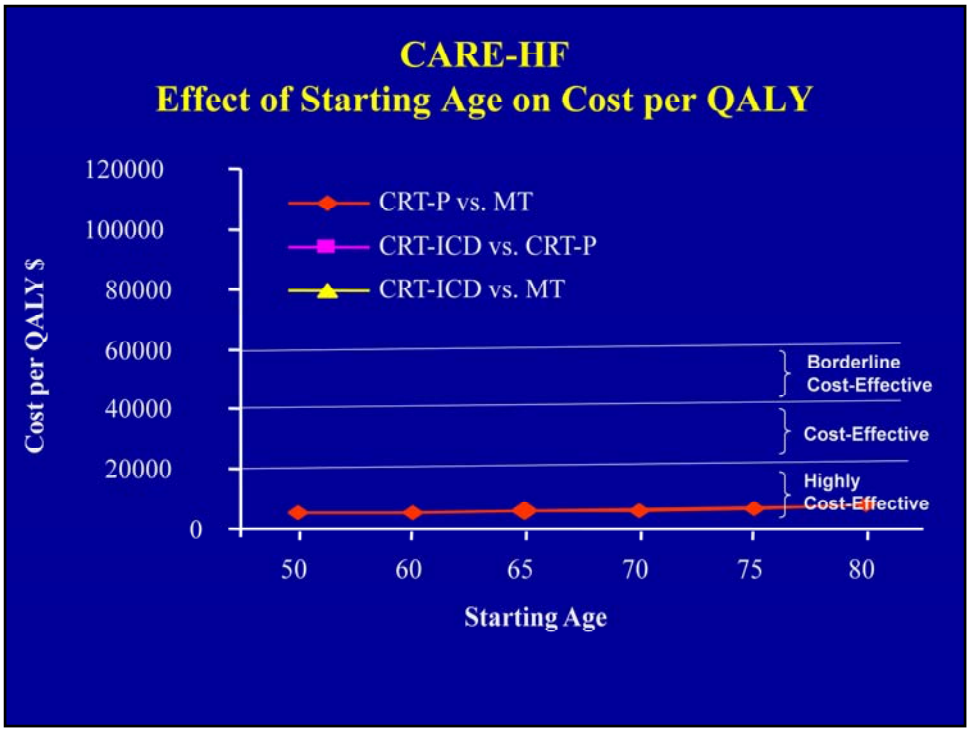

COMPANION
Use CRT
Use CRT
Use CRT
Use CRT


COMPANION
Use CRT
Use CRT
ICD prevent 1-2% deaths per year
CRT responsible for two-thirds
of reduction in mortality with CRT-D
Use CRT
Use CRT



This slide shows the effect of starting age on the Cost per QALY. The slide builds first showing the base case analysis results, and then showing the results for each starting age indicated. Starting age has no obvious effect upon the incremental cost per QALY for CRT-P which appears indicated in any age group meeting the criteria for the CARE-HF trial. However the cost per QALY increases over age for the comparison of CRT-ICD and MT, and dramatically so if we look at the incremental benefits of adding CRT-ICD to CRT-P.



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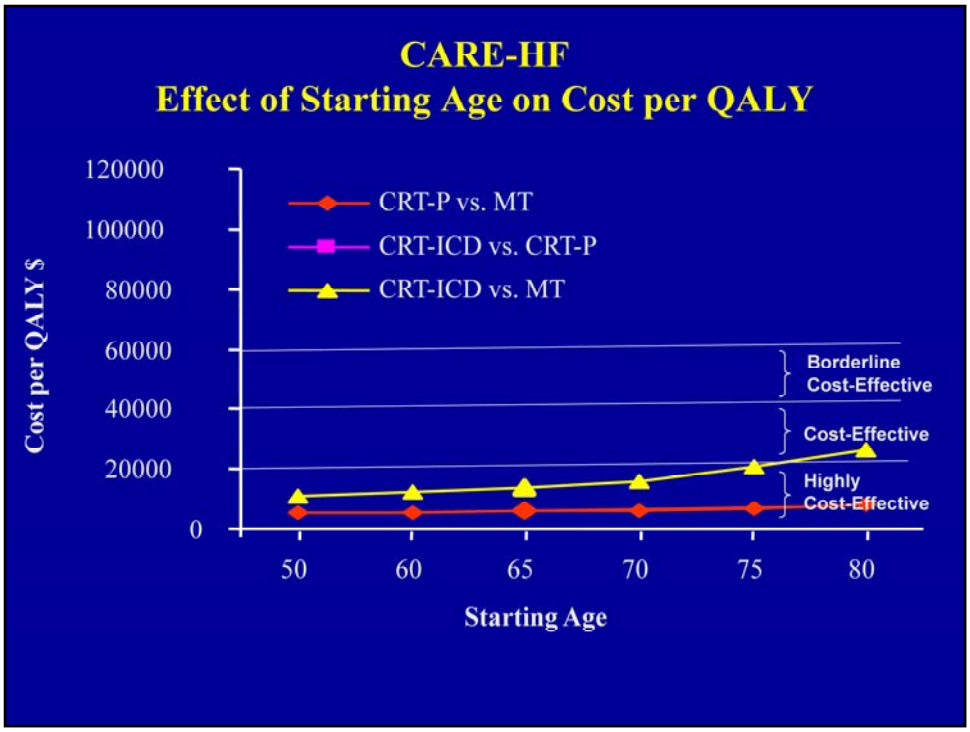

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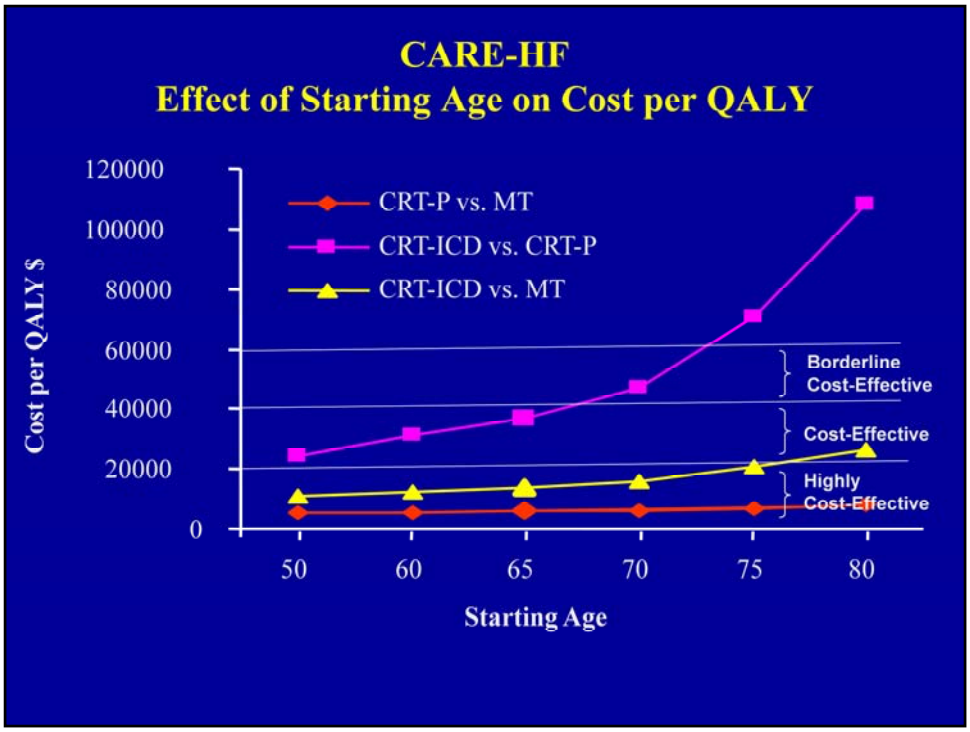

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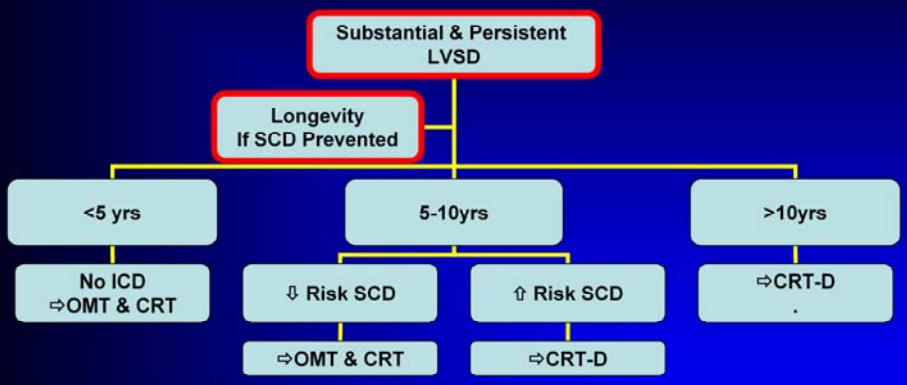
Selecting Patients for CRT / CRT-D



There is a very small role for ICDs
in the Management of Patients with Heart Failure

Conclusion

- No randomised controlled trial of CRT has ever shown that dyssynchrony is the substrate for the clinical benefits of CRT !
  - No good markers for responders / non-responders
  - Beware of surrogate endpoints!
- The only way to know if a patient (with a dilated LV) needs CRT is to try it
- If you are going to put a device in for heaven's sake (and those of the patient and the payer) try to get it right first time!

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